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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL I

Molecular mechanisms of anaesthesia: light at the end of the channel?

One hundred and fifty years after the first clinical use of chloroform, the molecular mode of action of general anaesthetics remains an enigma. This editorial highlights and discusses the significant advances made very recently in this field. Ligand-gated ion channels (LGIC), particularly the nicotinic receptor superfamily, have attracted much attention as model anaesthetic targets.[1] All members of this family (nicotinic, $5HT_3$, glycine, $GABA_A$) are thought to form fast ion channels by aggregating five subunits around a central hydrophilic pore (fig. 1).[2] This pentameric structure has been confirmed by electron microscopy which suggests that the channels gate (i.e. open when neurotransmitter is bound) by a relatively localized conformational change, confined to the core of the protein.[3] The macromolecular subunits themselves do not twist or distort their outer structure at the interface with the membrane bilayer. This in itself is of potential importance to anaesthetic researchers who have long sought an explanation for anaesthetic action in the lipophilic bulk membrane.[4] Lipid theories of anaesthetic action have been increasingly marginalized by researchers uncovering substantive evidence that proteins (first the globular luciferases then, increasingly, native or recombinant ion channels) can bear saturable stereoselective sites for modulation by "clinical concentrations" of a broad spectrum of anaesthetic drugs. Furthermore, these drugs exhibit the same structure–activity profiles, *in vitro* at the channel targets, as they do in patients.[5]

The inhibitory receptors activated by GABA have crucial roles in regulating arousal: GABA is used as a transmitter at up to one-third of all CNS synapses. The $GABA_A$ receptor probably represents the closest molecular species to a unifying target for general anaesthetics in the brain.[6] With the cloning of the receptor subunits throughout the 1980s and 1990s, we now know that there are many "isoforms" of the $GABA_A$ receptor expressed in the CNS.[7 8] Six GABA subunit classes have been cloned to date, with up to six homologues in each. In theory, there are well in excess of 100 000 different permutations for a functional pentameric receptor but, in practice, 20–30 functional combinations seems more likely.[7 8] These receptor isoforms can be expressed in oocytes or cell lines and subunit sensitivity of anaesthetic action has been sought for more than a decade. The direct agonist effects of barbiturates are demonstrably subunit-dependent but almost all functional (GABA-responsive) combinations could be modulated (inhibitory currents are enhanced in the presence of anaesthetics) by a range of anaesthetic drugs.[9] An interesting exception was the rho receptor originally characterized in the retina but also present at discrete sites in the brain. This homoligomeric receptor (functional pore made up of five identical subunits) was insensitive to, or antagonized by, volatile anaesthetics.[10] The epsilon subunit was the last to be cloned and its anaesthetic pharmacology was revealed in an article in *Nature* last year.[11] Co-expression of this subunit with alpha and beta appeared to totally ablate the anaesthetic sensitivity of the functional chloride channels. The physiological relevance of such a comparison is slightly obscure as there is very little evidence that receptors composed only of alpha and beta subunits exist in the brain. Just months later, sensitivity to barbiturates and steroids was reported for alpha+beta+epsilon receptors in the *Proceedings of the National Academy of Sciences (USA)*, based on similar experiments, highlighting the scope for contradictory, protocol-dependent research results from different laboratories.[12]

The availability of rare anaesthetic-insensitive (or unresponsive) cloned subunits for $GABA_A$ and glycine receptors cleared the way for mutagenesis studies and the construction of functional chimaeras. Large teams of multidisciplinary researchers then set about tracking the amino acid residues conferring sensitivity on the ion channel macromolecules. The elegant studies of Mihic and colleagues (again reported in *Nature*) revealed that specific residues in, or adjacent to, the $GABA_A$–glycine receptor ion channel lumen (in the plane of the membrane) conferred almost absolute sensitivity to two volatile anaesthetics and alcohol.[13] In the UK, Belelli and co-workers (in collaboration with Whiting and colleagues at Merck, Sharp and Dohme) applied a similar painstaking strategy to describe an almost identical locus for the modulatory actions of etomidate at recombinant human receptors.[14] Forman, Miller and Yellen had previously highlighted the importance of hydrophobic amino acids in the M2 channel domain for anaesthetic potency–affinity as antagonists of mutated nicotinic acetylcholine receptors.[15] Another study implicated the large extracellular N-terminus of nicotinic receptors in inhibition by volatile anaesthetics.[16] As all of these studies were conducted in the invariant membranes of expression systems, they emphasize the importance of protein structure for anaesthetic recognition and net effect. The fact that the channel proteins have not yet been crystallized for x-ray studies on their fine structure represents a major obstacle to further progress in this area. Such crystallographic techniques should demonstrate if anaesthetics bind to the implicated residues directly or if they are important only for allosteric coupling.

Will this exponential growth in understanding of molecular mechanisms lead to more effective or safer anaesthetic drugs? My personal view is that it will not. Anaesthetics are notoriously low-affinity and non-selective drugs which, I believe, underpins the

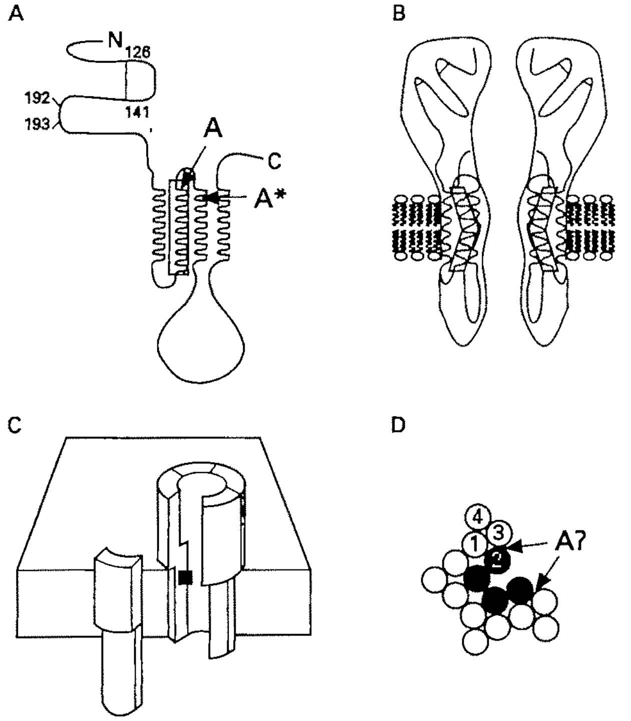

Figure 1 Proposed molecular structure of inhibitory ionotropic ($GABA_A$–glycine) receptors in the CNS. A. All ligand-gated ion channel subunits are made up of four putative transmembrane domains (left to right, M1–M4). The shaded transmembrane domain (M2, which forms the ion channel lumen) bears one of the novel anaesthetic sites (A).[13 14] The other anaesthetic–alcohol-sensitive site (A*) is on the M3 domain (arrowed). Both sites are near the extracellular side of the membrane. B: Simplified diagram showing the transmembrane topography of two subunits in the membrane. M2 is a kinked helix which projects a hydrophobic amino acid into the lumen, effectively acting as the gating mechanism (the channel opens by a relatively localized twisting of M2). Anaesthetics enhance the amplitude and duration of inhibitory chloride currents. C: Five subunits assemble in the membrane to form each functional ligand-gated channel as shown. Many isoforms exist throughout the CNS: six families of $GABA_A$ subunit have been cloned (α, β, γ, δ, ε, ρ: each with up to six structurally diverse members). The anaesthetic site is shown (square block) near the outer mouth of the channel. D: Putative orientation of transmembrane domains (the fifth subunit has been removed for clarity) in the membrane plane: M2 is a kinked amphiphilic helix. Domains 1, 3 and 4 are hydrophobic and more condensed (probably β-sheets). Anaesthetics (A) may bind to a site spanning two subunits as shown (although an allosteric effect on channel gating cannot be discounted).

agent-dependent spectrum of pharmacological and toxicological effects seen *in vivo*. Much of the recent interest in ligand-gated ion channels hinges on their sensitivity to clinical concentrations of anaesthetics. Voltage-gated channels and presynaptic processes were historically portrayed as relatively insensitive (being blocked only by heroic MAC-multiples). Much of these data were obtained in model (experimentally accessible) preparations such as the squid axon.[17] Now it is possible to study cloned voltage-gated Na^+ channels from humans under different conditions of neural discharge or in distinctive ionic environments.[18] Mammalian Na^+ channels can be significantly depressed by MAC-equivalent general anaesthetic concentrations if the cells are tonically depolarized or induced to fire rapidly.[19] This is analogous to the actions of local anaesthetic, antiarrhythmic and anticonvulsant drugs which promote channel inactivation and bind preferentially to depolarized–inactive channel conformations.

Ca^{2+} entry via voltage-gated channels (VGCC) is a key step in excitation–secretion coupling at presynaptic nerve terminals. A variety of anaesthetics have been shown to inhibit cardiovascular VGCC at relatively high concentrations, which may underpin the cardiodepressant and hypotensive actions of such drugs. Neural channels are also demonstrably sensitive to block by 1–4 MAC of isoflurane.[20] Much of the argument in favour of LGIC as *relevant model* anaesthetic targets hinges on their relatively high affinity for anaesthetics (EC_{50} or IC_{50} values are higher for VGCC).[1 21] This correlates better with MAC-equivalent concentrations of anaesthetics in patients at equilibrium. The VGCC experimenters, or independent reviewers,[22] argue that their data are physiologically relevant based on the very steep Ca^{2+} dependence of transmitter release.

The patch clamp technique is applicable even to the smallest mammalian nerve cell. The pioneering work of Takahashi and co-workers laid the foundations for impaling both presynaptic and postsynaptic cells in the same mammalian synapse.[23] Based on their experiments with metabotropic glutamate receptors, only a very small proportion of the presynaptic Ca^{2+} current needs to be inhibited to profoundly impair the transynaptic signal. This reinforces the potential importance of presynaptic Ca^{2+} entry for clinical anaesthetic effect. Only when anaesthetics have been quantitatively applied to such a model synapse (in combination with ionophoretic application of glutamate to gauge postsynaptic sensitivity) will the balance of pre- *vs* postsynaptic perturbation become apparent. To summarize, LGIC are only one of a series of anaesthetic-sensitive signalling proteins in the brain (voltage-gated K^+ channels, high-affinity uptake systems and ATPases, in addition to transporters, are demonstrably sensitive too). The NMDA glutamate receptor has long been acknowledged as a high affinity and stereoselective target for ketamine.[1]

How do we draw such disparate threads together? This has been attempted for many years by systems physiologists. Angel, painstakingly working *in vivo* on the reticular activating system, described selectively sensitive synaptic sites in the thalamic nuclei and in discrete cortical layers.[24] Based on the heterogenous effects of anaesthetics on firing pattern, he was then able to classify anaesthetic agents into three categories. Neither the anatomical selectivity nor the physiological classification appears to reflect what is known about the molecular actions of the drugs. A methodological constraint in these otherwise technically impressive and rigorous experiments is that the animals were already anaesthetized with urethane.

By working with slices maintained at 35°C in oxygenated artificial CSF, experimenters can now study the physiology of cells *in vitro* (without the need for background anaesthetic). The complex cyto-architecture of the slice is preserved and this technique has been invaluable in the elucidation of synaptic physiology and plasticity. Awareness and cognitive processes are associated with high frequency electrical oscillations in the cortex (approximately 40 Hz). It has been proposed that this reflects temporal binding of the different nuclei used to recognize a sensory stimulus (this occurs with virtually no phase lag). Synchronous binding of firing in different groups of cells throughout higher centres in the brain is therefore thought to underpin awareness and helps to filter the focus of our attention from the massive sensory bombardment with which we are continually faced. Whittington, Traub and Jefferys have since demonstrated that the synchronous 40-Hz activity in distinct primary relay cells in the hippocampus is generated by networks of inhibitory interneurones.[25] These are hard-wired to each other via GABA_A synapses and it is the kinetics of decay of the inhibitory chloride current (IPSC) which dictates oscillatory frequency.

Whittington, Traub and Jefferys have used this elegant system to examine the response to anaesthetic drugs. Barbiturates, benzodiazepines and a variety of induction agents (which have long been known to prolong IPSC) disrupt the frequency, as predicted by theoretical modelling and EEG profiles in anaesthesia.[26] Furthermore, Whittington's group (personal communication) have since shown distinct effects of opioids and dissociative anaesthetics (which respectively uncouple pyramidal cells from inhibitory networks or diminish the excitatory drive required to trigger interneuronal oscillators). Here then we have a systems level analysis which classifies drugs according to their physiological and molecular actions yet has a common end-point (perturbation of the oscillator) which appears to be relevant to cognition–arousal *in vivo*.

Significant progress has been made in the past decade. The increasing application of neurogenetic techniques resulting in animal strains devoid of (or ever-expressing) specific receptor subunits holds much promise to further advance (or refute) the above theories. This type of research requires collaboration between electrophysiologists, biochemists and molecular biologists, in addition to a huge investment in time, money and equipment (by research councils, charities and clinical colleagues–chairpersons). Despite the upbeat statements in grant applications, I find it difficult to see how this type of research can impact significantly on drug design even in the mid- to long-term future. The debates will continue to rage on the relevance (and rank order of importance) of specific proteins and signalling molecules but I think it is increasingly unlikely that a single unifying mechanism–target for anaesthetic action will emerge. Along the way, we are making an important contribution to molecular neuroscience. For a new generation of well-trained, committed neuropharmacologists, it will remain an intellectual challenge and *fun* to be involved!

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References

1. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature (London)* 1994; **367**: 607–614.
2. Lees G, Ortells MO, Lunt GG. Molecular biology and fine structure of ion channels: potential targets for general anaesthetics in the central nervous system. *Anaesthetic Pharmacology Review* 1994; **2**: 11–28.
3. Unwin N. Acetylcholine receptor channel imaged in the open state. *Nature (London)* 1995; **373**: 37–43.
4. Miller KW. The nature of the site of general anesthesia. *International Reviews in Neurobiology* 1985; **27**: 1–61.
5. Zimmerman SA, Jones MV, Harrison NL. Potentiation of γ-aminobutyric acid_A receptor Cl^- current correlates with *in vivo* anesthetic potency. *Journal of Pharmacology and Experimental Therapeutics* 1994; **240**: 987–991.
6. Tanelian DL, Kosek P, Mody I, MacIver MB. The role of the GABA_A receptor/chloride channel complex in anesthesia. *Anesthesiology* 1993; **78**: 757–776.
7. McKernan RM, Whiting PJ. Which GABA_A receptor subtypes really occur in the brain? *Trends in Neurosciences* 1996; **19**: 139–143.
8. Barnard EA. *The Molecular Biology of $GABA_A$ Receptors and their Structural Determinants in $GABA_A$ Receptors and Anxiety: from Neurobiology to Treatment.* New York: Raven Press, 1995; 1–16.
9. Harris RA, Mihic JS, Dildy-Mayfield JE, Machu TK. Actions of anesthetics on ligand-gated ion channels: role of receptor subunit composition. *FASEB Journal* 1995; **9**: 1454–1462.
10. Mihic SJ, Harris RA. Inhibition of ρ_1 receptor GABAergic currents by alcohols and volatile anesthetics. *Journal of Pharmacology and Experimental Therapeutics* 1996, **277**: 411–416.
11. Davies PA, Hanna MC, Hales TG, Kirkness EF. Insensitivity to anaesthetic agents conferred by a class of GABA_A receptor subunit. *Nature (London)* 1997; **385**: 820–823.
12. Whiting PJ, McAllister G, Vassilatis D, Bonnert TP, Heavens RP, Smith DW, Hewson L, Odonnell R, Rigby MR, Sirinathsinghji DJS, Marshall G, Thompson SA, Wafford KA. Neuronally restricted RNA splicing regulates the expression of a novel GABA(A) receptor subunit conferring atypical functional properties. *Journal of Neuroscience* 1997; **17**: 5027–5037.
13. Mihic JS, Ye Q, Wick MJ, Koltchine VV, Krasowski MD, Finn SE, Mascia MP, Valenzuela CF, Hanson KK, Greenblatt EP, Harris RA, Harrison NL. Sites of alcohol and volatile anaesthetic action on GABA_A and glycine receptors. *Nature (London)* 1997; **389**: 385–389.
14. Belelli D, Lambert JJ, Peters JA, Wafford K, Whiting PJ. The interaction of the general anesthetic etomidate with the gamma-aminobutyric acid type A receptor is influenced by a single amino acid. *Proceedings of the National Academy of Sciences USA* 1997; **94**: 11031–11036.
15. Forman SA, Miller KW, Yellen G. A discrete site for general anaesthetics on a postsynaptic receptor. *Molecular Pharmacology* 1995; **48**: 574–581.
16. Zhang L, Oz M, Stewart RR, Peoples RW, Weight FF. Volatile general anaesthetic actions on recombinant nACh (alpha 7), 5HT_3 and chimeric nACh-5-HT_3 receptors expressed in Xenopus oocytes. *British Journal of Pharmacology* 1997; **120**. 353–355.
17. Haydon DA, Elliott JR, Hendry BM, Urban BW. The action of nonionic anesthetic substances on voltage-gated ion conductances in squid giant axons. In: Roth I, Sheldon H, Miller KW, eds. *Molecular and Cellular Mechanisms of Anesthetics.* New York: Plenum, 1986.
18. Frenkel C, Duch DS, Urban BW. Effects of i.v. anaesthetics on human brain sodium channels. *British Journal of Anaesthesia* 1993; **71**: 15–24.
19. Rehberg B, Xiao Y-H, Duch DS. Central nervous system sodium channels are significantly suppressed at clinical concentrations of volatile anesthetics. *Anesthesiology* 1996; **84**: 1223–1233.
20. Study RE. Isoflurane inhibits multiple voltage-gated calcium currents in hippocampal pyramidal neurons. *Anesthesiology* 1994; **81**: 104–116.
21. Hall AC, Lieb WR, Franks NP. Insensitivity of P-type calcium channels to inhalational and intravenous general anesthetics. *Anesthesiology* 1994; **81**: 117–123.
22. Lynch C, Pancrazio JJ. Snails, spiders and stereospecificity—is there a role for calcium channels in anesthetic mechanisms? *Anesthesiology* 1994; **81**: 1–5.
23. Takahashi T, Forsythe ID, Tsujimoto T, Barnes Davies M, Onodera K. Presynaptic calcium current modulation by a metabotropic glutamate receptor. *Science* 1996; **274**: 594–597.
24. Angel A. Central neuronal pathways and the process of anaesthesia. *British Journal of Anaesthesia* 1993, **71**: 148–163.
25. Whittington MA, Traub RD, Jefferys JGR. Synchronised oscillations in interneurone networks driven by metabotropic glutamate receptor activation. *Nature (London)* 1995; **373**: 612–615.
26. Whittington MA, Jefferys JGR, Traub RD Effects of intravenous agents on fast inhibitory oscillations in the rat hippocampus *in vitro*. *British Journal of Pharmacology* 1996; **118**. 1977–1987.

British Journal of Anaesthesia 1998; 81: 494

EDITORIAL II

The Intensive Care Society and the *British Journal of Anaesthesia*

When it was founded in 1970, the Intensive Care Society was the first professional association in the world for physicians involved in intensive care. Since then it has grown year by year to a current membership in excess of 1100. Every year the society holds two excellent, well-attended meetings which include paper and poster presentations covering a wide range of research and audit topics related to intensive care. This issue of *British Journal of Anaesthesia*, for the first time, contains the abstracts from these sessions.

The journal has a long history of publishing abstracts of research presentations from anaesthetic specialist societies, such as the Anaesthetic Research Society, European Association of Cardiothoracic Anaesthesiologists and European Society of Anaesthesiologists. Although the journal has always published a considerable number of articles on intensive care topics, until now no abstracts from meetings primarily concerned with intensive care have appeared. This joint venture between the journal and the society thus breaks new ground, and is the beginning of a partnership which we hope will enhance the standing of research in the critically ill patient and the Intensive Care Society. This venture also underlines the continuing desire of the *British Journal of Anaesthesia* to publish quality peer-reviewed articles within this field. Of all journals specifically covering emergency and critical care medicine, only two American journals have significantly higher impact factors than the *British Journal of Anaesthesia*. Knowing that abstracts will be published in a major journal can only improve both the quality and number of abstracts submitted to the meetings, which is to the benefit of both the society and the journal.

The primary purpose of any journal is to make research findings available to its target audience. The *British Journal of Anaesthesia* is delivered monthly to the 80% of the membership of the Intensive Care Society who are fellows of the Royal College of Anaesthetists, and to more than 90% of the clinical directors of intensive care units. The journal is available in nearly every postgraduate library in the country. There is no other journal which could provide this combination of a high impact factor and near saturation coverage of the target audience.

The delay between the meetings and publication of these abstracts has been unacceptably long, and to avoid this problem in future the journal and the society have agreed a new procedure for abstract presentation, with an emphasis on electronic submissions. A similar system has worked very effectively for the Anaesthetic Research Society for several years, who kindly allowed us to copy the key elements of their process. The abstracts can now be longer and more detailed. Lack of space has caused a problem in the past, especially with tables and figures, and the preparation of the abstract booklet for the meetings should now be simplified. Publication of the abstracts will initially be funded by the journal; there will be no charge to authors and no drain on the society's charitable funds. The journal provides a similar service for the Anaesthetic Research Society.

At present, there is insufficient good quality intensive care research from UK centres to support a separate academic journal. However, the increasing recognition of intensive care as a specialty coupled with an expanding research base and increasing interest from funding bodies will soon improve this situation. In the fullness of time there may be enough research to support an academic journal of intensive care, possibly the official journal of the society. But until such time, the *British Journal of Anaesthesia* and Intensive Care Society will work together and doubtless will both benefit from the partnership.

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EDITORIAL NOTICE

An incident of DUAL PUBLICATION, involving the *British Journal of Anaesthesia* and the *European Journal of Surgery*, has recently been brought to the notice of the Editors-in-Chief of these two journals. It involves the following articles:

1. *British Journal of Anaesthesia* 1996; 77: 217–222. ASA classification and perioperative variables as predictions of postoperative outcome. U. Wolters, T. Wolf, H. Stutzer and T. Schroder.
2. *European Journal of Surgery* 1997; **163**: 563–568. Risk factors, complications, and outcome in surgery: A multivariate analysis. U. Wolters, T. Wolf, H. Stutzer, T. Schroder and H. Pichlmaier.

The authors wish to express their profound regret for the extensive duplication of data in these two articles and apologize unreservedly for their error.

British Journal of Anaesthesia 1998; **81**: 495–501

CLINICAL INVESTIGATIONS

Sevoflurane pharmacokinetics: effect of cardiac output†

J. F. A. HENDRICKX, A. A. J. VAN ZUNDERT AND A. M. DE WOLF

Summary

Sevoflurane uptake (V_{sevo}) can be predicted by the square root of time model or the four-compartment model. However, V_{sevo} and the effect of cardiac output on anaesthetic uptake have not been quantified clinically. After obtaining IRB approval and informed consent, 34 adult patients received closed-circuit anaesthesia with sevoflurane for 1 h. The end-expired sevoflurane concentration was maintained at 2.6% by infusion of liquid sevoflurane into the breathing system. In a subgroup of 12 patients, cardiac output was measured every 5 min by thermodilution (CO group). The effect of patient characteristics (age, height, weight, body surface area) and cardiac output on V_{sevo} were determined, and V_{sevo} was compared with the theoretical models. In the CO group, measured cardiac output was used in the formulae of these models. A two-exponential curve described average V_{sevo} well: V_{sevo} (ml liquid) $=0+1.62\times(1-e^{-2.3\times t})+18.1\times(1-e^{-0.0069\times t})$, $r^2>0.999$. There was no correlation between V_{sevo} and patient characteristics, except that V_{sevo} was greater in patients with a greater cardiac output ($r^2=0.36$) and cardiac index ($r^2=0.35$). The rate of sevoflurane uptake decreased less than predicted by the square root of time and four-compartment models, even when measured cardiac output was used in the formulae. These findings confirm that the square root of time and four-compartment models do not accurately predict anaesthetic uptake. In addition, uptake of sevoflurane cannot be predicted by patient characteristics but was higher in patients with a higher cardiac output. (*Br. J. Anaesth.* 1998; **81**: 495–501).

Keywords: anaesthetics volatile, sevoflurane, pharmacokinetics, sevoflurane; equipment, breathing systems

Theoretically, whole-body uptake of potent inhaled anaesthetics can be predicted from organ volume, organ blood flow and solubility of the anaesthetic in the organ.[1] After measurement of the solubility of these agents in various tissues and organs,[2] computer simulations were used to study anaesthetic uptake, leading to the development of uptake models such as the square root of time (SqRT) model[1] and the four-compartment (4C) model.[3] However, animal data indicate that the theoretical tissue time constants may not accurately describe organ uptake.[4] In addition, clinical data show that desflurane and isoflurane uptake are different from predictions based on these models.[5–8] It has been speculated that the discrepancies between the clinical observations and SqRT and 4C models are the result of factors such as changes in cardiac output (CO) with surgical stimulation or cutaneous and visceral losses.[9] However, the effect of CO on anaesthetic uptake has not been evaluated in humans. In addition, sevoflurane uptake (V_{sevo}) has not been quantified in humans.

Therefore, we have determined V_{sevo} using closed-circuit anaesthesia and investigated the relationship between V_{sevo} and CO, cardiac index (CI) and other patient characteristics. We also compared V_{sevo} with uptake predicted by the SqRT and 4C models using both calculated and measured CO in the formulae of these models.

Patients and methods

After obtaining approval from the hospital's Biomedical Institutional Review Board and informed consent, we studied 34 adult ASA I–III patients undergoing a variety of peripheral and abdominal procedures under general anaesthesia with sevoflurane in oxygen. Patient age, sex, height and weight were obtained, and body surface area (BSA) was calculated.

Premedication was adjusted to patient needs. After preoxygenation, anaesthesia was induced with propofol 2.5–3 mg kg^{-1} or etomidate 0.3 mg kg^{-1}. Tracheal intubation was facilitated by succinylcholine 1 mg kg^{-1} or vecuronium 0.08 mg kg^{-1}. Vecuronium was used to maintain neuromuscular block in all patients. After further denitrogenation (end-expired nitrogen concentration <3%), the circle system was closed and liquid sevoflurane was injected into the inspiratory limb of the circle system using a syringe pump with a volumetric accuracy of ±2%. An end-expired sevoflurane concentration of 2.6% (1.3 minimal alveolar concentration (MAC)) was achieved as rapidly as possible after the start of infusion of sevoflurane, and this end-expired concentration was maintained throughout the procedure by adjusting the infusion rate. Rapid vaporization of sevoflurane was ensured by heating the metal injection port using warm air, and visual inspection of the

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injection site revealed that after 5 min all liquid sevoflurane had vaporized. Oxygen flow was titrated to maintain the volume of the bellows constant. Ventilation was controlled and normocapnia was maintained throughout the procedure. Capnograms were normal in all patients, ensuring reliable end-expired sevoflurane concentrations. Hypotension, defined as a decrease in arterial pressure of more than 25% from baseline, was treated with i.v. fluid administration and ephedrine 5-mg boluses i.v. After 1 h, the circuit was opened and the study terminated.

Anaesthetic gas concentrations were monitored with a multi-gas analyser (Datex-Engstrom AS/3 Anesthesia Delivery Unit; Datex, Helsinki, Finland). The sampled gases (150–200 ml min^{-1}) were redirected into the system. ADU anaesthesia machines (Datex-Engstrom AS/3 Anesthesia Delivery Unit; Datex, Helsinki, Finland) were used with soda lime as the carbon dioxide absorber. Leak from the anaesthesia machine and breathing system during controlled mechanical ventilation with a peak inspiratory pressure of 30 cm H_2O was measured each morning using a self-test. The actual leak for each patient during the study was calculated based on the self-test and measured peak inspiratory pressure, and was 9–27 ml min^{-1}. All individual sevoflurane uptake data were corrected for this leak. The amount of liquid anaesthetic needed to load the anaesthesia system and an estimated functional residual capacity (FRC) of 2 litre with 2.6% sevoflurane was 1.3 ml of liquid sevoflurane. This dose is included in all data, curve fitting procedures and model predictions.

In a subset of 12 patients, CO and CI were measured by thermodilution after placement of a pulmonary artery catheter (CO group). CO and CI were measured just before the start of infusion of sevoflurane and every 5 min thereafter.

The cumulative sevoflurane dose (total amount of liquid anaesthetic injected over time) and end-expired anaesthetic concentrations were recorded every 1 min. Individual uptake curves and the average uptake curve were fitted to a series of mathematical models including, but not limited to, one- and two-exponential models (Table Curve 2D Automated Curve Fitting Software and Sigmaplot, Jandel, San Rafael, CA, USA). While a large number of equations accurately describe the uptake curves (r^2 >0.999), we chose one- or two-exponential functions, guided by goodness of fit (visual inspection and r^2 values, as calculated by the program), by simplicity of the function and by the fact that most biological processes behave exponentially. Exponential curve fitting yielded the following equations: $V_{sevo}=a_2+b_2\times(1-e^{-c_2\times t})$ (one-exponential fit); and $V_{sevo}=a_3+b_3\times(1-e^{-c_3\times t})+d_3\times(1-e^{-e_3\times t})$ (two-exponential fit). With the available data, the five parameters of the two-exponential fit could not be determined in all patients without the parameters becoming interdependent from one another. Because visual inspection revealed uptake at 3–60 min to be almost constant, and because the second time constant (112 min) of the two-exponential fit was so long relative to the duration of measurement (60 min), the individual uptake curves and the average uptake curve at 3–60 min were also fitted to a linear model: $V_{sevo}=a_1+b_1\times t$. The parameters of the individually fitted curves (b_1, b_2, c_2, b_3, c_3, d_3 and e_3) were correlated with patient characteristics and in the CO group with CO and CI using linear regression analysis. V_{sevo} was compared with uptake predicted by the SqRT and 4C models, using calculated CO (Brody's formula: $CO=0.2\times weight^{0.75}$ litre min^{-1}) in the total patient population and measured CO in the CO group. The formulae used to calculate uptake according to the SqRT and 4C models are presented in appendices A and B. Values are presented as mean (SD).

Results

Patient characteristics are shown in table 1. In two patients in the CO group, administration of sevoflurane was discontinued after 30 min because of hypotension, which was the result of excessive peripheral vasodilatation. Their uptake data for the first 30 min are included in the final data analysis. No patient developed clinical signs of renal dysfunction after operation.

Within 3–5 min, a constant end-expired sevoflurane concentration of 2.6% was obtained in all patients (fig. 1). There was significant inter-individual variation in V_{sevo}, with a coefficient of variation of 14–17 % over time. Sevoflurane cumulative doses after 5, 15, 30 and 60 min are presented in table 2. Individual linear, one-exponential and two-exponential curve fit parameters are presented in tables 3–5. A two-exponential curve was fitted in only 10 patients without the parameters becoming interdependent. The average uptake curve (fig. 2) was also fitted using linear, one-exponential and two-exponential models, yielding the following equations: V_{sevo} (ml liquid)=2.04+0.122×t (r^2=0.995) (the linear fit for 3–60 min); V_{sevo} (ml liquid)=1.34+14.29×$(1-e^{-0.013\times t})$ (r^2=0.993); and V_{sevo} (ml liquid)=0+1.62×$(1-e^{-2.3\times t})$+18.1×$(1-e^{-0.0089\times t})$ (r^2 >0.999). Because the amount of liquid anaesthetic needed to load the anaesthesia system and an estimated FRC of 2 litre with 2.6% sevoflurane was 1.3 ml, the a_2 intercept of the one-exponential fit and the sum of the a_3 intercept and b_3 of the two-exponential fit mainly reflected the anaesthesia system and FRC wash-in. b_1 (the slope of the linear fit) did not correlate with age (r^2=0.01), height (r^2 <0.01), weight (r^2=0.08) or BSA (r^2=0.05) (table 6). The correlations between the parameters b_2, c_2, b_3, c_3, d_3 and e_3 of the one- and two-exponential fitted curves and patient characteristics, CO and CI were not better than those between b_1 and the same characteristics. The SqRT and 4C models (based on calculated CO) overestimated average V_{sevo} during the initial part of the procedure (first 36 and 15 min, respectively), and underestimated average V_{sevo} thereafter (fig. 2). Similar observations were made in individual patients.

In the CO group, measured CO was remarkably stable (less than 5% variability over time) (fig. 3). Surgical incision did not affect CO. Average V_{sevo} in the CO group was similar to that in all 34 patients (fig. 4). b_1 in the CO group was 0.126 (0.021) and did not correlate with height (r^2 <0.01), weight (r^2=0.01) or BSA (r^2 <0.01) (table 6). A correlation was found between b_1 and age: b_1=−0.0422+0.0025×(age) (r^2=0.35). A higher CO and CI were associated with a higher b_1 (r^2=0.36 and r^2=0.35, respectively) (table 6, fig. 4). The correlations between the parameters of the one- and two-exponential fitted curves and patient characteristics, CO and CI were not better

Table 1 Patient characteristics with calculated cardiac output (COc) and cardiac index (CIc), and measured cardiac output (COm) and cardiac index (CIm). BSA=Body surface area

Patient No.	Sex	Age (yr)	Height (cm)	Weight (kg)	BSA (m^2)	COc (litre min^{-1})	CIc (litre min^{-1} m^{-2})	COm (litre min^{-1})	CIm (litre min^{-1} m^{-2})
1	M	17	185	64	1.85	4.50	2.44		
2	F	65	158	62	1.63	4.42	2.71	3.64	2.23
3	M	70	169	60	1.69	4.31	2.55		
4	M	62	169	72	1.82	4.94	2.71	3.83	2.10
5	F	52	165	86	1.93	5.65	2.92		
6	F	56	163	69	1.74	4.79	2.74		
7	F	24	153	67	1.65	4.68	2.85		
8	F	28	168	73	1.83	4.99	2.73		
9	M	67	182	79	2.00	5.30	2.65	4.83	2.41
10	F	75	155	68	1.67	4.74	2.83	4.80	2.87
11	F	63	166	60	1.67	4.31	2.59		
12	M	74	172	78	1.91	5.25	2.75	6.00	3.14
13	F	38	160	52	1.53	3.87	2.54		
14	M	64	170	69	1.80	4.79	2.66		
15	F	74	158	56	1.55	4.07	2.62	4.71	3.03
16	F	40	163	57	1.60	4.12	2.57		
17	M	50	186	70	1.93	4.84	2.51		
18	M	65	176	74	1.90	5.05	2.66	4.18	2.20
19	M	65	178	65	1.81	4.58	2.53	3.33	1.84
20	F	63	158	71	1.73	4.89	2.83	2.87	1.66
21	M	83	170	63	1.73	4.47	2.58		
22	M	34	171	58	1.68	4.20	2.51		
23	M	66	174	74	1.88	5.05	2.68	4.61	2.44
24	F	67	160	61	1.63	4.37	2.67		
25	F	47	164	60	1.65	4.31	2.61		
26	M	68	174	86	2.01	5.65	2.81	3.59	1.79
27	F	45	156	67	1.67	4.68	2.81		
28	F	26	160	71	1.74	4.89	2.81		
29	F	53	156	75	1.75	5.10	2.91		
30	F	59	157	50	1.48	3.76	2.54		
31	F	39	168	72	1.82	4.94	2.72		
32	F	24	169	65	1.75	4.58	2.62		
33	M	65	187	65	1.88	4.58	2.44		
34	F	60	165	65	1.71	4.58	2.68	5.39	3.15
Mean		54.4	167.2	67.1	1.75	4.68	2.67	4.31	2.41
(SD)		(17.2)	(9.2)	(8.5)	(0.13)	(0.44)	(0.13)	(0.91)	(0.53)

than those between b_1 and the same characteristics. When measured CO data were used in the formulae of the theoretical models, the SqRT and 4C models still overestimated average V_{sevo} during the initial part of the procedure (first 32 and 18 min, respectively), and underestimated uptake thereafter (fig. 5); the same was true for individual patients.

Discussion

A two-exponential curve fitted the average V_{sevo} very well for procedures up to 1 h. The relatively long time constant (112 min) of the second exponential function of the two-exponential curve fit indicated that after the 3–5-min wash-in period, the rate of sevoflurane uptake over time changed little during the first hour. In addition, the rate of sevoflurane uptake, or V_{sevo} per unit time (ml liquid min^{-1}), decreased less than predicted by the SqRT and 4C models, even when measured CO was used in the formulae of these models. The rate of uptake of isoflurane and desflurane also decreased significantly less than predicted by the SqRT model.[5–8] It has been speculated that the discrepancies between the clinical observations and SqRT and 4C models are the result of factors such as changes in CO with surgical stimulation, or cutaneous and visceral losses.[9] However, we found that CO did not fluctuate significantly in this clinical study using sevoflurane anaesthesia. After substituting measured CO values in the formulae, both models overestimated uptake during the initial part of the procedure and underestimated it thereafter. Although a higher CO and CI were associated with higher sevoflurane uptake, we found that the correlation between CI and b_1 (r^2=0.35) was no better than the correlation between CO and b_1 (r^2=0.36). Preliminary data for desflurane uptake appear to confirm these findings.[8] Visceral and percutaneous losses are minimal and probably cannot account for the differences between our data and the theoretical models.[10 11] Although soda lime absorbs and degrades

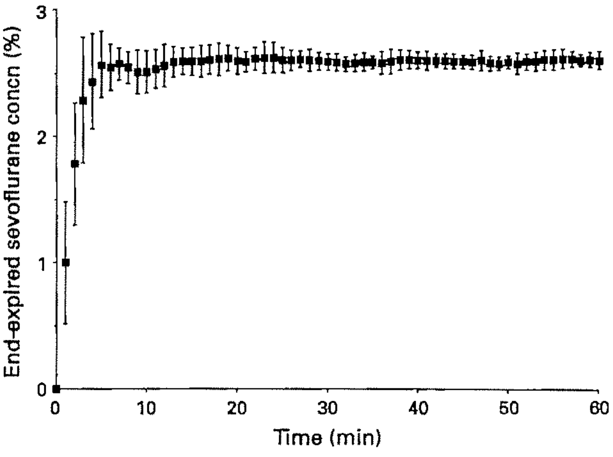

Figure 1 End-expired sevoflurane concentration over time in all 34 patients (mean, SD).

Table 2 Cumulative dose of sevoflurane (CDsevo) after 5, 15, 30, 45 and 60 min. †Based on 30-min observations

Patient No.	CD_{sevo} 5 (ml)	CD_{sevo} 15 (ml)	CD_{sevo} 30 (ml)	CD_{sevo} 45 (ml)	CD_{sevo} 60 (ml)
1	2.6	3.6	4.9	6.2	7.3
2	2.2	3.5	5.3	6.6	8.3
3	2.7	4.2	5 9	7.5	8.9
4	2.9	5.3	7.2	9 3	11.3
5	2.6	4.2	6.3	7.9	9.5
6	2.7	4.1	5.7	7.0	8.7
7	3 5	5.2	7.4	9.1	11.2
8	3.1	4.4	6.9	8.9	11.3
9	2.2	3.8	5.9	7.7	9.4
10	2 3	3.6	5.8	7.9	9.9
11	2.3	3.7	5.5	6.6	7.7
12	1 8	3.7	5.8	8.4	10 2
13	2.6	3.4	4.9	6.3	7.6
14	2.1	3.4	5.3	6.6	7.8
15	2.0	3.7	6.2	8.3	10.2
16	2.4	4.0	5.8	7.8	9.6
17	2.6	5.0	7.6	10.3	12 5
18	2.3	4.1	6.2	7.8	9.2
19†	2.2	3.2	5.0		
20	2.1	3.1	4.7	6.0	7.4
21	2.1	3.6	6.0	8.1	10.1
22	2.7	3.5	4.7	6.2	7.3
23†	2.2	3.7	5.3		
24	2.1	3.6	5.6	6.9	8.2
25	1.9	3.3	4.9	6.4	7.9
26	2.1	3.5	5.0	6 3	7.9
27	2.4	5.0	7.5	9.8	12.1
28	2.8	4.8	6 4	7.8	9.4
29	2.4	4.7	6.4	8.8	11.2
30	2.0	3.2	5.1	6.5	7.7
31	2.5	4.8	6.8	8.8	10.4
32	2.4	3.6	4.8	6.1	7.3
33	2.5	3.7	5.3	6.6	7.8
34	2.0	3.5	5.4	6.8	7.9
Mean (SD)	2.4 (0.4)	3.9 (0.6)	5.8 (0.8)	7.5 (1.2)	9.1 (1.5)

Table 3 Linear fit parameters ($V_{sevo}=a_1+b_1 \times t$) based on 3–60-min observations. †Based on 3–30-min observations

Patient No.	a_1 (ml)	b_1 (ml min^{-1})	r_2
1	2.301	0.086	0.994
2	1.956	0.106	0.990
3	2.345	0.114	0 992
4	2.663	0.149	0.985
5	2.393	0.123	0.990
6	2.376	0.105	0.990
7	3.079	0.136	0.992
8	2.247	0.151	0.998
9	1.854	0.128	0.995
10	1.545	0.141	0.999
11	2.385	0.094	0.967
12	1.107	0.158	0.997
13	2.092	0.093	0.996
14	1.828	0.105	0.991
15	1.473	0.152	0.995
16	1.800	0.130	0.997
17	2 101	0.180	0.995
18	2.091	0.126	0.986
19†	1.503	0.117	0.994
20	1.690	0.096	0.998
21	1.519	0.145	0.997
22	2.051	0.090	0.997
23†	1.662	0.132	0.993
24	1.987	0.110	0.980
25	1.782	0.102	0.994
26	1.860	0.100	0.994
27	2.168	0.169	0.991
28	2.884	0.111	0.979
29	2.089	0.150	0.996
30	1.673	0.107	0.990
31	2.371	0.142	0.986
32	2.180	0.087	0.997
33	2.414	0.093	0.985
34	1.853	0.108	0.986
Mean (SD)	2.039 (0.416)	0.122 (0 .025)	0.991 (0.007

Table 4 One-exponential fit parameters ($V_{sevo}=a_2+b_2\times(1-e^{-c_2\times t})$). †Based on 30-min observations

Patient No.	a_2 (ml)	b_2 (ml)	c_2 (min^{-1})	r_2
1	1.5	8.5	0.018	0.979
2	1.3	11.9	0.014	0.990
3	1.5	11.8	0.016	0.989
4	1.6	15.1	0.016	0.988
5	1.5	12.5	0.016	0.990
6	1.5	10.4	0.018	0.984
7	1.9	13.7	0.017	0.984
8	1.8	33.2	0.006	0.989
9	1.3	17.0	0.011	0.993
10	1.3	51.9	0.003	0.994
11	1.2	7.6	0 028	0.989
12	0.7	33.5	0.006	0.997
13	1.4	10.5	0.014	0.983
14	1.2	11.0	0.015	0.993
15	1.4	10.5	0.014	0.983
16	1.3	20.2	0.008	0.993
17	1.3	24.0	0.011	0.996
18	1.1	11.9	0.019	0.995
19†	1.0	6.8	0.028	0.961
20	1.3	14.1	0.009	0.989
21	1.1	24.1	0.008	0.996
22	1.7	16.7	0.007	0.977
23†	1.0	6.2	0.040	0.968
24	1.1	10.0	0.020	0.993
25	1.2	12.6	0.012	0.988
26	1.3	11.8	0.013	0.988
27	1.2	18.7	0.014	0.996
28	1.6	9.5	0.025	0.984
29	1.6	31.0	0.006	0.989
30	1.1	11.8	0.014	0.992
31	1.3	13.5	0.018	0.993
32	1.6	10.2	0.013	0.979
33	1.5	8.4	0.021	0.982
34	1.0	10.4	0.018	0.994
Mean (SD)	1.33 (0.26)	15.62 (9.56)	0.015 (0.007)	0.987 (0.008)

Table 5 Two-exponential fit parameters ($V_{sevo}=a_3+b_3\times(1-e^{-c_3\times t})+d_3\times(1-e^{-e_3\times t})$)

Patient No.	a_3 (ml)	b_3 (ml)	c_3 (min^{-1})	d_3 (ml)	e_3 (min^{-1})	r^2
1	0.1	2.1	0.647	16.7	0.00618	0.999
3	0.0	1.9	2.183	14.6	0.01099	0.999
5	0.0	1.8	2.257	14.9	0.01184	0.998
6	0.5	2.0	0.796	15.3	0.00909	0.996
7	0.0	2.6	0.893	20.3	0.00877	0.997
13	0.0	1.9	0.762	23.5	0.00451	0.999
14	0.0	1.4	2.657	12.8	0.01177	0.999
31	0.0	1 6	2.875	14.9	0.01475	0.998
32	0.0	2.0	1.918	18.0	0.00577	0.999
33	0.0	1.9	1.294	10.3	0.01379	0.996
Mean (SD)	0.07 (0.16)	1.91 (0.33)	1.628 (0.847)	16.12 (3.76)	0.00975 (0.00347)	0.9980 (0.0011)

sevoflurane, we calculated that approximately 0.2 ml h^{-1} of liquid sevoflurane would be absorbed and degraded under our study conditions, which is approximately 2% of the total uptake of sevoflurane after 1 h in this study.[12] Sevoflurane undergoes biodegradation, but this amount is only a fraction (approximately 3%) of total body uptake.[13]

There are other indications that the SqRT and 4C models may not be accurate, as recent observations suggest that some of the underlying assumptions used in the uptake models may be incorrect or incomplete. The SqRT and 4C models assume that arterial partial pressures equal alveolar partial pres-

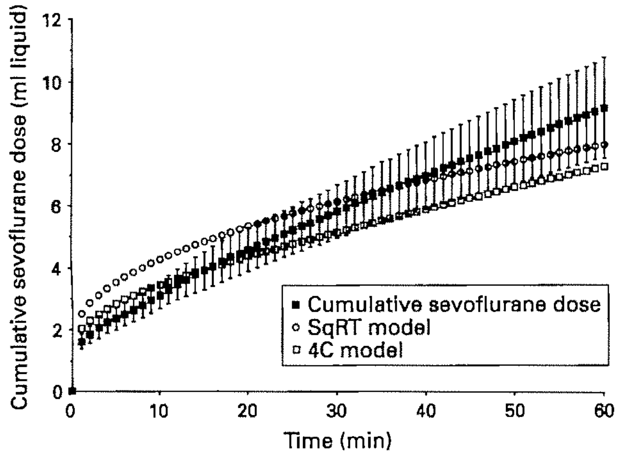

Figure 2 Cumulative sevoflurane dose (mean, SD ml liquid) in all 34 patients and cumulative dose, as predicted by the square root of time (SqRT) and four-compartment (4C) models, using calculated cardiac output in the formulae of these models.

sures.[1,3] This may be the basis of significant error, because a significant arterial to end-expired gradient for isoflurane has been described in humans, caused by deadspace ventilation, shunting and diffusion limitations.[14] The arterial to end-expired partial pressure ratio was 0.66 after end-expired isoflurane partial pressure had been stable for at least 15 min.[14] In addition, the theoretical models calculate whole body anaesthetic uptake based on the uptake of each individual organ, which can be determined from the volume of the organ, tissue solubility of the agent and organ perfusion.[1,3] Assuming organ uptake is an exponential process when arterial concentration is constant, a time constant can be calculated for each organ or tissue group. However, brain time constants of desflurane, isoflurane and halothane in rabbits obtained *in vivo* differ significantly from the theoretically calculated values.[4] Tissue–gas partition coefficients determined on tissue homogenates from cadavers[15] may not represent solubility of an anaesthetic in an organ *in vivo*. Reported values for tissue–gas partition coefficients for isoflurane differ by up to 150% between studies, and the coefficient of variation for isoflurane tissue–gas partition coefficient is up to 150% (for muscle–gas partition coefficient) between patients.[15] In addition, regional blood flows used in the theoretical models may not be accurate. Finally, the theoretical models may not account for uptake by anatomically or functionally less well defined "tissue groups". Also, inter-tissue diffusion may be a factor affecting uptake and distribution of inhaled anaesthetics, but it is unclear how this affects total body uptake.[16–18] These arguments indicate that

Table 6 Correlations (r_s) between b_1 and patient characteristics, CO, and CI. b_1 represents the slope of the linearly fitted curve of sevoflurane uptake between 3 and 60 min BSA=Body surface area, CO=cardiac output, CI=cardiac index

	All patients	CO group
Age	0.01	0.35
Height	<0.01	<0.01
Weight	0.08	0.01
BSA	0.05	<0.01
CO	—	0.36
CI	—	0.35

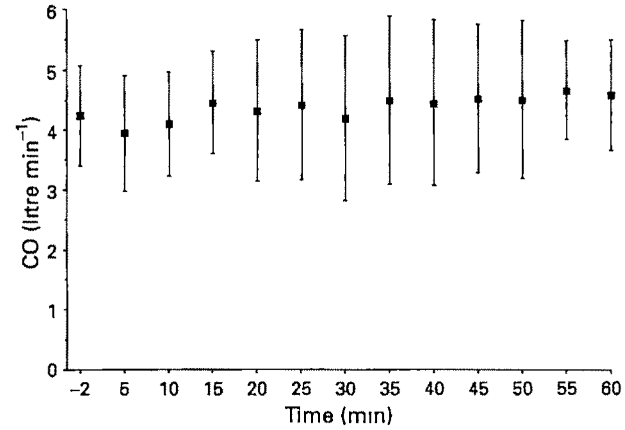

Figure 3 Measured cardiac output (CO) in a subgroup of 12 patients (CO group) (mean, SD).

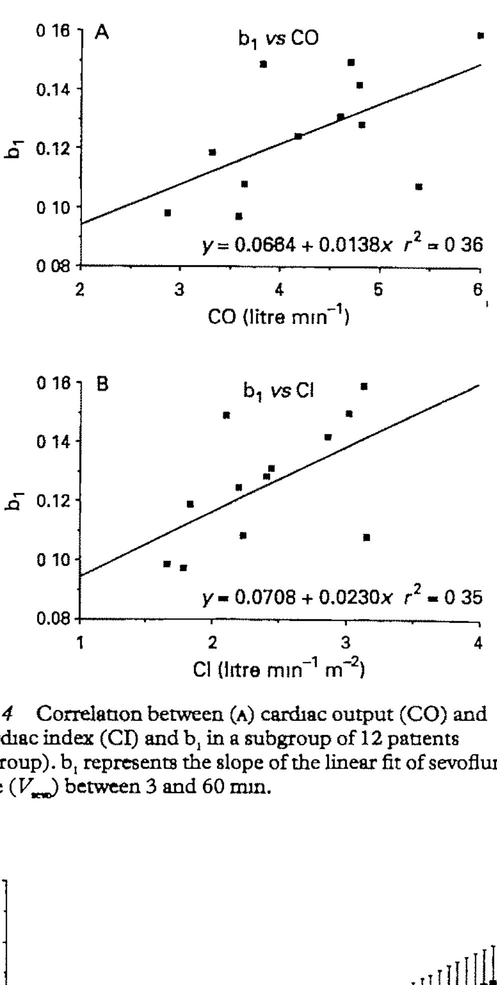

Figure 4 Correlation between (A) cardiac output (CO) and (B) cardiac index (CI) and b_1 in a subgroup of 12 patients (CO group). b_1 represents the slope of the linear fit of sevoflurane uptake (V_{sevo}) between 3 and 60 min.

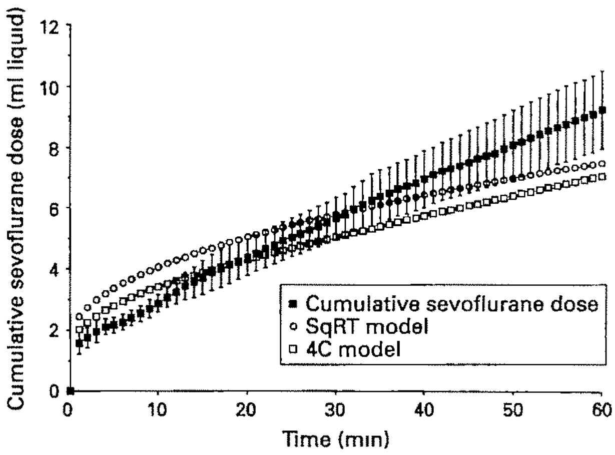

Figure 5 Cumulative sevoflurane dose (mean, SD ml liquid) in a subgroup of 12 patients (CO group), and cumulative dose, as predicted by the square root of time (SqRT) and four-compartment (4C) models using measured cardiac output in the formulae of these models

many steps along the partial pressure cascade of potent inhaled anaesthetics are poorly studied. Even though more sophisticated uptake models exist, they lack sufficient experimental validation.[19–22]

Our observations have several implications. First, quantification of whole body uptake is important because it forms the basis for the general anaesthetic equation which determines vaporizer settings over time with different fresh gas flows to maintain a constant end-expired concentration.[1] The relatively long time constant (112 min) of the second exponential function of the two-exponential curve fit of the average V_{sevo} implies that after the desired end-expired concentration has been obtained and maintained for approximately 5 min, the changes in vaporizer setting are minimal for the remainder of the anaesthetic, even if low-flow or closed-circuit anaesthesia is used. The increasing availability of anaesthetic gas monitoring and introduction of agents with a low blood–gas partition coefficient may further facilitate low-flow anaesthesia. Second, current computer programs simulating anaesthetic uptake may not be correct because they are based on theoretical models, although these programs may still be useful to teach some basic principles of anaesthetic uptake. Pharmaco-economical studies comparing the costs of different agents and evaluating the cost–effectiveness of future automated low-flow and closed-circuit anaesthesia machines should use real uptake data. Third, we could not find any correlation between V_{sevo} and patient weight, height or BSA. Even though some authors found weak correlations,[23] most authors did not.[5 6 8 24] At the tissue level, no correlation was found between tissue–gas solubilities and age (except for a correlation between age and desflurane muscle–gas partition coefficient, with $r^2=0.59$).[15] Automated feedback-controlled administration of inhaled anaesthetics in future anaesthesia delivery systems based on low-flow and closed-circuit anaesthesia may provide a clinical solution for inter-individual variation in anaesthetic uptake. Fourth, Eger has described that when the inspired concentration is kept constant, the alveolar concentration of an inhaled anaesthetic increases more slowly when CO is greater because anaesthetic uptake is greater.[5] We also found that anaesthetic uptake is greater with a greater CO, but in our study design the end-expired concentration was kept constant, and hence the rate of increase in alveolar concentration was dependent on the speed of injection and vaporization of the agent only. While a greater CO may slow induction (defined as the rate of rise of *brain* concentration) with the former technique (constant inspired concentration) and hasten induction with the latter (constant end-expired concentration), this has yet to be proved *in vivo*. When using the closed-loop feedback technique to maintain the end-expired concentration constant, the rate of increase in *alveolar* concentration of an inhaled anaesthetic becomes independent of both cardiac output and blood–gas solubility of the agent.

We limited this study to 1 h because more data are needed to define the clinically safe combinations of fresh gas flow, sevoflurane concentration and duration of administration. While closed-circuit anaesthesia with sevoflurane up to 3–5 h was found previously to be safe,[25] more recent data urge caution because of the accumulation of possible nephrotoxic sevoflurane degradation products.[26] Studies using closed-circuit anaesthesia to determine V_{sevo} during prolonged procedures will have to be delayed until this issue has been clarified.

In summary, the SqRT and 4C models were inaccurate in their prediction of V_{sevo}, and their accuracy did not improve when measured CO was used in the calculations. V_{sevo} cannot be predicted by patient characteristics but was greater in patients with a higher cardiac output.

Appendix A

SEVOFLURANE UPTAKE ACCORDING TO THE SQUARE ROOT OF TIME MODEL OF LOWE AND ERNST[1]

During closed-circuit anaesthesia, uptake of a potent inhaled anaesthetic has been predicted by the SqRT model.[1] A "unit dose" is taken up by the body during the first minute and during each subsequent time interval (3 min, 5 min, 7 min, 9 min, 11 min, 13 min, etc.). In addition, the "prime dose" is required to saturate the circuit, functional residual capacity (FRC) and arterial delivery system. The addition of the prime dose and unit dose over time result in the "cumulative dose".

(1) Unit dose (litre of vapour)$=2\times f\times \mathrm{MAC}\times\lambda_{B/G}\times Q$

(2) Prime dose (litre of vapour)$=f\times \mathrm{MAC}\times\lambda_{B/G}\times Q+\mathrm{Vol}\times f\times \mathrm{MAC}$

(3) Cumulative dose (litre of vapour)=prime dose+unit dose$\times\sqrt{t}=f\times \mathrm{MAC}\times\lambda_{B/G}\times Q+\mathrm{Vol}\times f\times \mathrm{MAC}+2\times f\times \mathrm{MAC}\times\lambda_{B/G}\times Q\times\sqrt{t}$

(4) Conversion of vapour into liquid: 1 litre vapour$=\mathrm{MW}/(24\times \mathrm{D})$ litre liquid

where f=fraction of MAC administered (in this study 1.3); MAC=minimal alveolar concentration (for sevoflurane 2%); $\lambda_{B/G}$=blood–gas partition coefficient (for sevoflurane 0.6); Q=cardiac output (CO, litre min^{-1}), *calculated*, based on Brody: $\mathrm{CO}=0.2\times\mathrm{weight\ (kg)}^{0.75}$: 4.68 (0.44) litre min^{-1} ($n=34$), and *measured*, in the CO group: 4.36 (0.18) litre min^{-1} ($n=12$); t=time (min); $\sqrt{t}$=square root of time; Vol=volume of circuit and FRC (litre); MW=molecular weight (for sevoflurane 200); D=density (for sevoflurane 1.505×10^3 g litre^{-1}).

Appendix B

SEVOFLURANE UPTAKE ACCORDING TO THE FOUR-COMPARTMENT MODEL OF EGER[3]

Anaesthetic uptake by an organ at constant arterial concentration can be calculated when the size of the organ, solubility of the anaesthetic vapour in the organ and organ perfusion are known.[1 2] Organs and tissues are grouped into VRG, MG, FG and VPG (vessel-rich group, muscle group, fat group and vessel poor group, respectively). VPG is ignored in the calculations because its contribution to uptake during the first hour is small and because sevoflurane solubility in these tissues has not been determined. The amount of liquid anaesthetic needed to load the anaesthesia breathing system and an estimated functional residual capacity (FRC) of 2 litre with 2.6% sevoflurane was 1.3 ml of liquid sevoflurane. This dose is included in the model prediction.

(1) Organ capacity (litre vapour)$=f\times \mathrm{MAC}\times\lambda_{T/G}\times V_O$

(2) Organ time constant (t, min)$=(V_O\times\lambda_{T/B})/Q_O$

(3) Organ uptake (litre vapour min^{-1})=amount delivered$\times$ fraction absorbed$=(C_a\times10\times Q_O)\times e^{-t/\tau}$

(4) Cumulative organ uptake (litre vapour)$=(f\times \mathrm{MAC}\times\lambda_{T/G}\times V_O)\times(1-e^{t/\tau})$

where V_O=organ volume (litre); Q_O=organ blood flow (litre min^{-1}); τ=organ time constant (min); $\lambda_{T/G}$=tissue–gas partition coefficient (see Laster and colleagues[10]); $\lambda_{T/B}$=tissue–blood partition coefficient (see Laster and colleagues[10]); C_a=arterial concentration ($f\times \mathrm{MAC}\times\lambda_{B/G}$).

In table 1A, we present the information that was used to calculate V_{sevo} according to the four compartment model for all 34 patients combined and for the subgroup of 12 patients in which CO was measured invasively.[1 3 15] $\lambda_{B/G}=0.6$; $3\times\tau$ gives 95% organ saturation.

Table 1A V_{sevo} according to the four-compartment model for all 34 patients combined and for the subgroup of 12 patients in which cardiac output (CO) was measured invasively.[1 3 15] $\lambda_{b/a}$=0.6; 3×τ gives 95% organ saturation. MG=Muscle group, FG=fat group

	Brain	Liver	Heart	Kidney	Blood	MG	FG
$\lambda_{t/a}$	1.70	1.85	1.78	1.15	—	3.13	47.5
$\lambda_{t/b}$	1.15	1.25	1.21	0.78	0.6	2.38	34.0
All patients combined							
V_0 (litre)	1.41	3.82	0.27	0.27	4.70	28.58	10 07
Organ capacity (ml liquid)	0.23	0.69	0.05	0.03	0.38	9.77	49.16
Organ blood flow (Q_0, litre min^{-1})	0.74	1.41	0.22	1.19	—	0.59	0.22
τ (min)	3.23	5.02	2.18	0.26	—	151	2174
CO group							
V_0 (litre)	1.49	4.04	0.28	0.28	4.96	30.16	10.62
Organ capacity (ml liquid)	0.25	0.72	0.05	0.03	0.40	10.31	51 87
Organ blood flow (Q_0, litre min^{-1})	0.69	1.31	0.21	1.10	—	0.55	0.21
τ (min)	3.66	5.70	2.37	0.30	—	171	2402

References

1. Lowe HJ, Ernst EA. *The Quantitative Practice of Anesthesia—Use of Closed Circuit.* Baltimore: Williams and Wilkins, 1981.
2. Lowe HJ. Flame ionization detection of volatile organic anesthetics in blood, gases and tissues. *Anesthesiology* 1964; **25**: 808–814.
3. Eger EI II. *Anesthetic Uptake and Action.* Baltimore/London: Williams and Wilkins, 1974.
4. Lockhart SH, Cohen Y, Yasuda N, Freire B, Taheri S, Litt L, Eger EI II. Cerebral uptake and elimination of desflurane, isoflurane, and halothane from rabbit brain: an *in vivo* NMR study. *Anesthesiology* 1991; **74**: 575–580.
5. Lockwood GG, Chakrabarti MK, Whitwam JG. The uptake of isoflurane during anaesthesia. *Anaesthesia* 1993; **48**: 748–752.
6. Hendrickx JFA, Soetens M, Van der Donck A, Meeuwis H, Smolders F, De Wolf AM. Uptake of desflurane and isoflurane during closed-circuit anesthesia with spontaneous and controlled mechanical ventilation. *Anesthesia and Analgesia* 1997; **84**: 413–418.
7. Walker TJ, Chakrabarti MK, Lockwood GG. Uptake of desflurane during anaesthesia. *Anaesthesia* 1996; **51**: 33–36.
8. Hendrickx JFA, De Wolf AM. Desflurane uptake during liver transplantation and liver resection using closed-circuit anesthesia. *Anesthesia and Analgesia* 1997; **84**: S497.
9. Eger EI II. Complexities overlooked: things may not be what they seem. *Anesthesia and Analgesia* 1997; **84**: 239–240.
10. Laster MJ, Taheri S, Eger EI II, Liu J, Rampil IJ, Dwyer R. Visceral losses of desflurane, isoflurane, and halothane in swine. *Anesthesia and Analgesia* 1991; **73**: 209–212.
11. Fassoulaki A, Lockhart SH, Freire BA, Yasuda N, Eger EI II, Weiskopf RB, Johnson BH. Percutaneous loss of desflurane, isoflurane, and halothane in humans. *Anesthesiology* 1991; **74**: 479–483.
12. Morio M, Fujii K, Satoh N, Imai M, Kawakami U, Mizuno T, Kawai Y, Ogasawara Y, Tamura T, Negishi A, Kumagai Y, Kawai T. Reaction of sevoflurane and its degradation products with soda lime. *Anesthesiology* 1992; **77**: 1155–1164.
13. Shiraishi Y, Ikeda K. Uptake and biotransformation of sevoflurane in humans: a comparative study of sevoflurane with halothane, enflurane, and isoflurane. *Journal of Clinical Anesthesia* 1990; **2**: 381–386.
14. Landon MJ, Matson AM, Royston BD, Hewlett AM, White DC, Nunn JF. Components of the inspiratory–arterial isoflurane partial pressure difference. *British Journal of Anaesthesia* 1993; **70**: 605–611.
15. Yasuda N, Targ AG, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. *Anesthesia and Analgesia* 1989; **69**: 370–373.
16. Perl W, Rackow H, Salanitre E, Wolf G, Epstein RM. Intertissue diffusion effect for inert fat-soluble gases. *Journal of Applied Physiology* 1965; **20**: 621–627.
17. Cohen EN, Chow KL, Mathers L. Autoradiographic distribution of volatile anesthetics within the brain. *Anesthesiology* 1972; **37**: 324–331.
18. Strum DP, Eger EI II, Unadkat JD, Johnson BH, Carpenter RL. Age affects the pharmacokinetics of inhaled anesthetics in humans. *Anesthesia and Analgesia* 1991; **73**: 310–318.
19. Lockwood GG, White DC. Effect of ventilation and cardiac output on the uptake of anaesthetic agents from different breathing systems: a theoretical study. *British Journal of Anaesthesia* 1991; **66**: 519–526.
20. Yasuda N, Lockhart SH, Eger EI II, Weiskopf RB, Johnson BH, Freire BA, Fassoulaki A. Kinetics of desflurane, isoflurane, and halothane in humans. *Anesthesiology* 1991; **74**: 489–498.
21. Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. Pharmacokinetics of inhaled anesthetics in humans: measurements during and after the simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide. *Anesthesia and Analgesia* 1986; **65**: 575–582.
22. Lerou JGC, Dirksen R, Beneken Kolmer HH, Booij LHD. A system model for closed-circuit inhalation anesthesia. I. Computer study. *Anesthesiology* 1991; **75**: 345–355.
23. O'Callaghan AC, Hawes DW, Ross JAS, White DC, Wloch RT. Uptake of isoflurane during clinical anaesthesia Servo-control of liquid anaesthetic injection into a closed-circuit breathing system. *British Journal of Anaesthesia* 1983; **55**: 1061–1064.
24. Westenskow DR, Jordan WS, Hayes JK. Uptake of enflurane: a study of the variability between patients. *British Journal of Anaesthesia* 1983; **55**: 595–601.
25. Bito H, Ikeda K. Closed-circuit anesthesia with sevoflurane in humans. Effects on renal and hepatic function and concentrations of breakdown products with soda lime in the circuit. *Anesthesiology* 1994; **80**: 71–76.
26. Eger EI II, Koblin DD, Bowland T, Ionescu P, Laster MJ, Fang Z, Gong D, Sonner J, Weiskopf RB. Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. *Anesthesia and Analgesia* 1997; **84**: 160–168.

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Spinal anaesthesia for paediatric day-case surgery: a double-blind, randomized, parallel group, prospective comparison of isobaric and hyperbaric bupivacaine

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Summary

We have compared bupivacaine 5 mg ml^{-1}, either isobaric in saline 0.9% or hyperbaric in 8% glucose, for spinal anaesthesia in 100 children, aged 2–115 months, in a double-blind, randomized, parallel group, prospective study. Children were premedicated with diazepam 0.5 mg kg^{-1} orally. Seventy-two children were sedated before, and 25 children after, lumbar puncture, with either propofol or thiopental (thiopentone). After lumbar puncture in the lateral decubitus position with a 24–27-gauge paediatric spinal needle, isobaric or hyperbaric bupivacaine 5 mg ml^{-1} was injected in a dose of 0.3–0.5 mg kg^{-1} using a blinded procedure. Maximum cephalad extent of the block was tested by transcutaneous electrical stimulation. The success rate of the block was greater with hyperbaric bupivacaine (96%) compared with isobaric bupivacaine (82%) (P=0.025, 95% confidence intervals (CI) 0–28%). Intense motor block was associated with adequate sensory block. Spread and duration of sensory block showed a similar wide scatter in both groups. The highest median level of sensory block was T4 (range T1–12) in the isobaric group and T4 (T1–7) in the hyperbaric group. Times to two segment regression of block were similar: 80 (55–190) min in the isobaric and 80 (30–190) min in the hyperbaric group. Cardiovascular stability was good. Etilefrin was administered to one child to treat hypotension and atropine to one child to treat bradycardia. The study gave an impression of a delayed onset time of spinal block, as most of the nine children who required either fentanyl or a sedative for a mild reaction to skin incision had complete block when transferred to the recovery room after operation. Five children developed a mild, position-dependent headache. (*Br. J. Anaesth.* 1998; **81**: 502–506).

Keywords: anaesthetic techniques, subarachnoid; anaesthetic local, bupivacaine; children; anaesthesia, paediatric; anaesthesia, day-case; physics, baricity

Spinal anaesthesia produces rapid onset, profound and uniformly distributed analgesia with good neuromuscular block. Spinal anaesthesia permits the use of a small dose of local anaesthetic with a low risk of toxicity. The amide local anaesthetics are used regularly for spinal anaesthesia in children, and of these bupivacaine and lidocaine (lignocaine) are used almost exclusively.[1] However, the duration of action of intrathecally injected lidocaine may be too short in some children undergoing paediatric day-case surgery.[2]

Bupivacaine is an amide local anaesthetic with a moderately rapid onset and a long duration of action. It is highly protein bound and metabolized mostly in the liver. For spinal anaesthesia, bupivacaine is most commonly used as an isobaric or hyperbaric solution. Isobaric bupivacaine is formulated using normal saline as a diluent, with a specific gravity of 1.000 at 37°C. Hyperbaric bupivacaine in 8% glucose has a specific gravity of 1.021 at 37°C.[3] Both isobaric and hyperbaric bupivacaine have been used for spinal anaesthesia in children with good results.[2,4] The hyperbaric solution has been administered more frequently: the isobaric solution has received less attention.[5,6] These two bupivacaine solutions have not been compared previously in children.

The aim of our study was to compare the use of isobaric and hyperbaric bupivacaine for spinal anaesthesia in paediatric day-case surgery. We assessed quality and spread of analgesia and anaesthesia, time to regression of sensory block by two dermatomes, total time to recovery from block and time required to reach the criteria for discharge from hospital.

Patients and methods

The study was approved by the Ethics Committee of Kuopio University Hospital and conducted in accordance with the Declaration of Helsinki. Parents of the patients and children old enough to understand the study gave informed consent. We studied 100 children, ASA I–II, aged 2–115 months, undergoing day-case surgery. Patients with known contraindications to spinal puncture, such as increased intracranial pressure, haemorrhagic diathesis or infection at the puncture site were excluded. Children with a neurological disorder or allergy to bupivacaine or other local anaesthetics were also excluded.

We used a double-blind, randomized, parallel group, prospective study design. Patients were allocated randomly to receive spinal anaesthesia with either isobaric (in normal saline) or hyperbaric (in 8% glucose) bupivacaine 5 mg ml^{-1} (Astra, Sweden). A block randomization method of four children at a time was used to keep the number of subjects

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balanced in the two groups. A dose of 0.5 mg kg^{-1} was used for children less than 10 kg, 0.4 mg kg^{-1} for children weighing 11–19 kg and 0.3 mg kg^{-1} for those more than 20 kg. The doses selected were based on previous studies with spinal anaesthesia where children weighing less than 10 kg needed more bupivacaine than those weighing more than 20 kg to achieve the same height and duration of block.[24] Commercial ampoules with erased drug names were prepared and coded in the hospital pharmacy. Their identical appearance allowed blinding of the study. One study ampoule (No. 48) was accidentally broken. The next ampoule and study number were used for that child. The pharmacy prepared a new No. 48 ampoule which was used for the next child who entered the study and was coded as study No. 48.

Children were not allowed solid food or milk products for 4–6 h before anaesthesia. Clear fluids were allowed up to 2 h before induction of anaesthesia. Each child was premedicated with diazepam 0.5 mg kg^{-1} orally, up to a maximum dose of 10 mg. EMLA cream was used at the lumbar and venepuncture sites. An infusion consisting of 0.9% saline was given at 10 ml kg^{-1} h^{-1}. Children breathed room air spontaneously for as long as Sp_{O_2} remained >90%. I.v. ketoprofen 2 mg kg^{-1} or rectal paracetamol 40 mg kg^{-1}, or both, was given for pre-emptive pain treatment.

Intraoperative monitoring consisted of non-invasive arterial pressure measurements every 5 min, continuous ECG, ventilatory frequency, peripheral arterial oxygen saturation (Sp_{O_2}) and end-tidal carbon dioxide concentration, using a nasal adapter. Appropriate treatment was given if systolic arterial pressure decreased to less than 75% of preoperative levels, if heart rate decreased to less than 75% of baseline, if the Sp_{O_2} decreased to less than 90% breathing room air or if end-tidal carbon dioxide partial pressure increased to more than 7 kPa. All adverse effects were recorded.

Children who were anxious or felt uncomfortable after premedication or during operation were sedated with an i.v. bolus of thiopental (thiopentone) 2–3 mg kg^{-1} followed by 1 mg kg^{-1} as needed, or propofol 0.5–1 mg kg^{-1} followed by infusion of 2–4 mg kg^{-1} h^{-1}. Sedation was used in 97 children (74 children received propofol and 23 thiopental). Sedated children had a similar distribution in both groups. Seventy-two children were sedated before, and 25 after, lumbar puncture, with a similar frequency in each group. The most common reason for sedation was the young age of the child (79 cases). Seven children were sedated because they were anxious and 11 children expressed the wish to be sedated during operation. All sedated children were monitored closely by the anaesthetist or by an anaesthetic nurse using intraoperative monitoring.

All spinal blocks were performed by the same anaesthetist (H. K.). Lumbar puncture was performed in the lateral decubitus position using a midline approach at the L3–4 or L4–5 interspace. Paediatric spinal needles (50-mm long, 25-gauge Quincke; 25-mm long, 26-gauge Atraucan; 37-mm long, 27-gauge Whitacre; or 35-mm long, 24-gauge Sprotte) without an introducer were used for spinal puncture. The bevel of the needle was facing laterally, parallel to the longitudinal dural fibres. Correct placement of the spinal needle was verified by free flow of cerebrospinal fluid (CSF). After injection of local anaesthetic, free back flow of CSF was again verified and the child was placed in the supine, horizontal position.

If there were signs of inadequate anaesthesia (reaction to skin incision, increase in heart rate, arterial pressure or ventilatory frequency) i.v. fentanyl or general anaesthesia was given for supplementary analgesia. This was recorded and the case designated as failed spinal block.

An electric stimulator (Microstim Plus, Neuro Technology, Houston, TX, USA) was used to evaluate the width of the analgesic area, 15 and 30 min after injection of the anaesthetic. The metal electrodes of the device were moved in a rostral direction along the surface of the trunk using continuous high-frequency stimulation (50 Hz, pulse width 0.2 ms, amplitude 30–60 mA) until the patient responded, indicating the upper border of the anaesthetic area. Amplitude was adjusted to the lowest level so that the response could just be elicited. The procedure was repeated until the level of the first unanaesthetized segment was confirmed. Motor block was assessed using a modified Bromage scale recording the child's ability to flex the ankle, knee and hip (0=no motor block, 3=complete motor block of the legs and feet).

After operation, children were transferred to the post-anaesthesia care unit (PACU) for continuous monitoring of vital signs and regression of block. Time to regression of block by two segments was tested every 5 min and the time recorded. All adverse effects were recorded. If the child was in pain, fentanyl 1 μg kg^{-1} i.v. was given and the time recorded.

Patients were discharged from hospital when they were awake, able to walk unaided, had stable vital signs for at least 1 h, no pain or only mild pain, no nausea or vomiting and were able to tolerate clear fluids. Time to reach these criteria was recorded.

Power analysis suggested that 48 children would be needed in each group for a 90% chance at the 0.05 level of significance of detecting a 10% difference in success rate between groups. Statistical tests used for categorical data were chi-square test and Fisher's exact test. For continuous data, analysis of variance (ANOVA) and Student's *t* test were applied to test the significance between means. Linear association between independent variables was tested by Pearson's correlation. Results are presented as mean (SD), median, number (%) of cases and range or 95% confidence intervals for differences (95% CI), as appropriate. The level of significance was set at $P<0.05$.

Results

The groups were comparable in patient characteristics (table 1), procedures performed (table 2) and in the characteristics of spinal puncture (table 3).

The success rate of spinal block was higher in the hyperbaric compared with the isobaric group ($P=0.025$, 95% CI for difference 0–28%) (table 4). One child in the isobaric group did not develop sensory block and was excluded from analysis.

There was wide variation in cephalad spread of sensory block in both groups (table 5). Cephalad

Table 1 Patients characteristics. Data are mean (SD), median [range] or number

	Isobaric bupivacaine (n= 50)	Hyperbaric bupivacaine (n= 50)
Sex (M/F)	43/7	41/9
Weight (kg)	15 (6) 13 [6–28]	15 (5) 14 [6–26]
Height (cm)	94 (20) 90 [58–129]	94 (19) 91 [58–134]
Age (months)	29 [2–115]	27 [3–96]
ASA I/II	36/14	39/11

Table 2 Number of operations performed in the two groups

Operation	Isobaric bupivacaine (n= 50)	Hyperbaric bupivacaine (n= 50)
Herniotomy	18	27
Circumcision	3	3
Orchidopexy	11	6
Urological	4	2
Orthopaedic	8	3
Plastic surgery	6	9

Table 3 Characteristics of spinal puncture in the two groups. Data are number of cases or median [range]

	Isobaric bupivacaine (n= 50)	Hyperbaric bupivacaine (n= 50)
Bupivacaine (mg kg^{-1})	0.45 [0.3–0.5]	0.45 [0.3–0.5]
Interspace used for spinal puncture		
L3-4	18	12
L4-5	32	38
Repeated skin punctures	7	5
Redirection of needle	12	8
Appearance of CSF at the hub (s)	2 [1-20]	2 [1-5]
Time to complete the block (s)	25 [5-240]	30 [10–62]

spread of anaesthesia did not correlate with the age of the child or dose of bupivacaine used.

In the isobaric group, time to regression of sensory block by two dermatomes correlated with the interspace used for spinal puncture (r=0.35, P=0.025). In the hyperbaric group, there was no such correlation (r=0.07, P=0.65). There was no correlation between regression of block by two dermatomes and height of the initial block in either the hyperbaric (r=0.35, P=0.053) or isobaric (r=0.28, P=0.13) group.

Table 4 Success rate of the spinal anaesthesia in the two groups. Data are number of cases (%). *P= 0.025, chi-square-test, 95% CI for difference, 0–28%. †One case, after an initially complete block after 75 min

	Isobaric bupivacaine (n= 50)	Hyperbaric bupivacaine (n= 50)
Sensory block		
Complete	41 (82%)	48 (96%)*
Failure	9 (18%)	2 (4%)
General anaesthesia	2 (4%)†	
Fentanyl i.v.	3 (6%)	1 (2%)
Sedative i.v.	4 (8%)	1 (2%)
Motor Block		
Complete	39 (95%)	45 (96%)
Some movement	2 (5%)	2 (4%)

Table 5 Characteristics of sensory block in the two groups. Data are median [range]. Times are after spinal puncture

	Isobaric bupivacaine (n= 49)	Hyperbaric bupivacaine (n= 50)
Height of sensory block (dermatome)	T4 [T1–T12]	T4 [T1–T7]
Time to two segment regression of block (min)	80 [55–190]	80 [30–190]
Time to first dose of rescue analgesic (min)	125 [55–420]	110 [53–270]
Time to discharge from hospital	220 [100–425]	205 [120–315]

Duration of sensory block did not correlate with either dose of bupivacaine or age of the child.

Fentanyl was administered to 52 children in the PACU for analgesia: 27 (55%) in the isobaric group and 25 (50%) in the hyperbaric group (table 5). Time to the first dose of analgesic was similar in both groups.

Oxygen was administered to two children in the isobaric group and to eight in the hyperbaric group because Sp_{O_2} decreased to less than 90%. One child in the hyperbaric group was given one dose of etilefrin (Effortil, Boehringer Ingelheim, Ingelheim am Rhein, Germany) during operation for hypotension. One child in the isobaric group was administered atropine in the PACU to treat bradycardia. One child in the isobaric group and three children in the hyperbaric group experienced shivering in the PACU. There were no differences between groups in the incidence of adverse effects.

All children met the criteria for discharge from hospital within 7 h after spinal puncture. Median time was 220 min in the isobaric group and 205 min in the hyperbaric group. Three children in the isobaric group and two in the hyperbaric group developed a position-dependent headache with a duration of 1–3 days. One child also had stiffness in the neck, nausea, vomiting and fever. All headaches were mild and no epidural blood patches were performed.

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Discussion

In this study, the success rate of spinal anaesthesia was high with both isobaric and hyperbaric bupivacaine. One spinal anaesthetic failed and general anaesthesia was required. In another, spinal anaesthesia was converted to general anaesthesia because surgery outlasted the duration of sensory block. As neither thiopental nor propofol have analgesic properties at subanaesthetic doses,[7] the use of light sedation did not mask possible failed blocks. Sedatives are required frequently during regional anaesthesia, and this is especially true in small children, to produce a calm, compliant patient. However, deep sedation is contraindicated as the presence of paraesthesia during needle placement may not be identified, increasing the risk of persistent neurological injury.[8]

Several techniques have been used in children to assess the width of sensory block, such as reaction to skin incision, cold stimulus with ice, presence of pinprick or touch sensation, and somatosensory evoked potentials.[2,4,9–11] In this study, transcutaneous electrical stimulation (TES) was used to measure the anaesthetic area achieved with spinal block. TES has been found to be equivalent to surgical incision.[12] TES is a reproducible stimulus and may be better than pinprick for assessment of height and duration of surgical anaesthesia in sedated children. However, it is most important to reduce the amplitude to the lowest possible to avoid unnecessary distress.

Onset of spinal block with bupivacaine in infants has been reported to be fast (<2 min).[10] In this study, onset time was not measured. However, the impression was that in the age group 1–7 yr, onset time was prolonged as most of the nine children in whom fentanyl or a sedative was administered because of mild reactions to skin incision, had complete block by the end of surgery. In adults, Sanderson and colleagues[13] observed that onset of spinal block with bupivacaine in 8% glucose was faster than that with plain bupivacaine. This may also be true in children, as more supplementation was needed in the isobaric group. The possible slow onset time of spinal block must be taken into account when test doses are used in epidural anaesthesia in children. Delayed spinal anaesthesia may develop but still not be complete after 30 min.[14] Onset time of sensory block with intrathecal bupivacaine in children needs further study.

Spread and duration of anaesthesia were similar but variable and unpredictable with both isobaric and hyperbaric bupivacaine. In other studies using bupivacaine for spinal anaesthesia in children, a similar variability has been shown.[2,4] With bupivacaine 0.3 mg kg^{-1}, the mean upper level of sensory block was one segment lower than in our study.[14] In children aged 1–5 yr given bupivacaine 0.4 mg kg^{-1}, spread of anaesthesia was similar but duration of block was shorter compared with our study.[4] In a study using isobaric bupivacaine 0.5 mg kg^{-1}, mean segmental spread of sensory block was T3 after 15 min and had reached T2 after 45 min.[9] However, duration of block was similar to our study. Mitchell and co-workers[15] compared hyperbaric and isobaric bupivacaine in adults at a dose of 0.42 mg kg^{-1}. They found no differences between the groups in mean spread or duration of spinal block but the upper level of block varied widely from C8 to T11 with both solutions.

The degree of motor block in this study was similar to that in previous studied in children[4,10] and adults,[13,15] confirming that spinal anaesthesia with bupivacaine produces adequate relaxation for surgery below the umbilicus. However, as the shortest duration of sensory block may be less than 60 min, the anaesthetist must always be prepared to deal with inadequate block and be able to convert to general anaesthesia if the surgery is prolonged and outlasts the block.

Cardiovascular alterations, hypotension and bradycardia, are normal physiological responses during spinal anaesthesia because of sympathetic fibre block.[16] In children, cardiovascular stability during spinal anaesthesia is good.[6,10,11] It has been recommended that Sp_{O_2} should remain >94%.[17] However, in 10% of children, Sp_{O_2} decreased to less than 90% on room air. This emphasizes the necessity for appropriate respiratory monitoring and administration of supplementary oxygen in all patients undergoing surgical procedures under regional anaesthesia with sedation. In addition, it is our practice to monitor ventilation by measuring end-tidal carbon dioxide partial pressure using a nasal adaptor.

In summary, we have demonstrated that the use of spinal anaesthesia in paediatric day cases was associated with a 10% failure rate and a relatively low incidence of adverse effects. However, further work is required to determine if the use of spinal anaesthesia alone in children undergoing day-case surgery is associated with fewer adverse effects compared with general anaesthesia.

References

1. McNicol R Paediatric regional anaesthesia. an update In: Lindahl S, ed. *Paediatric Anaesthesia*. London Baillière Tindall, 1996; 725–752.
2. Kokki H, Hendolin H. Comparison of 25G and 29G Quincke spinal needles in paediatric day case surgery. A prospective randomized study of the puncture characteristics, success rate and postoperative complaints. *Paediatric Anaesthesia* 1996; **6**· 115–119.
3. AFHS Drug Information 97 McEvoy GK, ed Bethesda: American Society of Hospital Pharmacists, 1997
4. Kokki H, Hendolin H, Maunuksela E-L, Vainio J, Nuutinen L. Ibuprofen in the treatment of postoperative pain in small children. A randomized double-blind-placebo controlled parallel group study. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 467–472.
5. Sethna NF, Berde CB. Paediatric regional anaesthesia. In. Gregory GA, ed *Paediatric Anaesthesia*. New York: Churchill Livingstone, 1994; 281–317
6. Bang-Vojdanovski B. 10 Jahre Spinalanasthesie bei Saugligen und Kindern inder orthopadischen Chirurgie. Ein klinischer Erfahrungsbericht. *Anaesthesist* 1996; 45 271–277.
7. Jewett BA, Gibbs LM, Tarasiuk A, Kendig JJ Propofol and barbiturate depression of spinal nociceptive neurotransmission. *Anesthesiology* 1992; 77· 1148–1154.
8. Horlocker TT, McGregor DG, Matsushige DK, Schroeder DR, Besse JA A retrospective review of 4767 consecutive spinal anesthetics. central nervous system complications. *Anesthesia and Analgesia* 1997; 84: 578–584
9 Kokki H, Hendolin H, Vainio J, Partanen J Operation im Vorschulalter Vergleich von Spinalanästhesie und Allgemeinanasthesie. *Anaesthesist* 1992; 41. 765–768.
10. Mahe V, Ecoffey C. Spinal anesthesia with isobaric bupivacaine in infants. *Anesthesiology;* 1988; **68**: 601–603.
11. Saint-Maurice C. Spinal block. In: Saint-Maurice C, Steinberg OS, eds. *Regional Anaesthesia in Children*. Fribourg, Switzerland· Mediglobe SA, 1990, 119–125.

12. Petersen-Felix S, Zbinden AM, Fischer M, Thomson DA Isoflurane minimum alveolar concentration decreases during anesthesia and surgery. *Anesthesiology* 1993; **79**: 959–965.
13. Sanderson P, Read J, Littlewood DG, McKeown D, Wildsmith JAW. Interaction between baricity (glucose concentration) and other factors influencing intrathecal drug spread. *British Journal of Anaesthesia* 1994; **73**: 744–746.
14. Kokki H, Hendolin H. Comparison of spinal anaesthesia with epidural anaesthesia in paediatric surgery. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 896–900.
15. Mitchell RWD, Bowler GMR, Scott DB, Edstrom HH. Effects of posture and baricity on spinal anaesthesia with 0.5% bupivacaine 5 ml. A double-blind study. *British Journal of Anaesthesia* 1988; **61**: 139–143.
16. Covino BG, Scott DB, Lambert DH. *Handbook of Spinal Anaesthesia and Analgesia.* Fribourg, Switzerland: Mediglobe SA, 1994.
17. Nolan DM. Procedural safety. In: Whitwam JG, McCloy RF, eds. *Principles and Practice of Sedation*. Oxford: Blackwell Science, 1998; 73–90.

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Comparison of epidural bolus administration of 0.25% bupivacaine and 0.1% bupivacaine with 0.0002% fentanyl for analgesia during labour

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Summary

We have compared analgesia during labour provided by two epidural drug regimens, in a double-blind, randomized, controlled study. Group A received 10-ml bolus doses of 0.1% bupivacaine with fentanyl 2 μg ml^{-1} while group B received 0.25% plain bupivacaine 10 ml. Analgesia provided by both techniques was similar, but women in group A retained motor power in their legs and 60% chose to get out of bed. Duration of labour and time from insertion of the epidural to delivery was similar in both groups, but in group A, duration of the second stage was significantly shorter (P=0.0003; 95% confidence interval (CI) −1.17, −0.27 h) and the incidence of forceps delivery was lower (P=0.032). Maternal satisfaction with epidural analgesia, as assessed by VAS, was higher in group A (P=0.04; 95% CI −0.001, 10.001). (*Br. J. Anaesth.* 1998; **81**: 507–510).

Keywords: analgesia, obstetric; analgesic techniques, epidural; anaesthetics local, bupivacaine; analgesics opioid, fentanyl

Despite providing excellent pain relief during labour, epidural analgesia using local anaesthetic agents alone produces motor block in up to 85% of patients,[1] reduces maternal satisfaction with analgesia,[2] and is associated with a prolonged second stage and increased incidence of instrumental delivery.[3] Epidural opioids offer the possibility of analgesia without motor block but when used alone do not provide satisfactory analgesia throughout labour.[4 5] Adding an opioid to local anaesthetic solutions can provide effective analgesia with bupivacaine sparing and a reduction in motor block.[2 6–8] However, most investigators have used a high concentration of local anaesthetic (usually 0.25% bupivacaine) to initiate analgesia, or a larger test dose, for example 1.5–2% lidocaine (lignocaine) or 0.5% bupivacaine, both of which contribute to motor block.[7 9] Similarly, the use of epidural infusions may hinder maternal mobility.

Collis and colleagues pioneered the "mobile" epidural using a combined spinal–epidural technique. Analgesia is established with intrathecal bupivacaine 2.5 mg and fentanyl 25 μg, and maintained with epidural top-ups of 0.1% bupivacaine and fentanyl 0.0002%[10 11]; almost 50% of women are able to get out of bed at some point during labour.[10] However, problems associated with this technique include technical failure, post-dural puncture headache[10 11] and chemical meningitis.[12]

The aim of this study was to compare, in a double-blind, randomized study, a mobile epidural using 0.1% bupivacaine and 0.0002% fentanyl with a conventional epidural using 0.25% bupivacaine throughout labour.

Patients and methods

After obtaining approval from the Hospital Ethics Committee and written informed consent, we studied 80 women requesting epidural analgesia in labour. Women who had been given systemic opioids within 4 h of epidural request were excluded, as were those with cervical dilatation greater than 4 cm.

I.v. access was secured but no i.v. fluid load was given. An epidural catheter was sited at the second lumbar interspace using a standard midline technique with an 18-gauge Tuohy needle. The study was double-blind, with randomization (computer-generated numbers) and preparation of the epidural drug solutions performed by the hospital pharmacy. Women were allocated randomly to one of two groups. In group A, analgesia was established with 15 ml of 0.1% bupivacaine with fentanyl 50 μg and maintained, on maternal request, with bolus doses of 10 ml of 0.1% bupivacaine with fentanyl 2 μg ml^{-1}. In group B, analgesia was established with 15 ml of 0.25% plain bupivacaine and maintained with 10-ml bolus doses of 0.25% plain bupivacaine.

Analgesia was measured using visual analogue scores (VAS) on a 100-mm line and a verbal scoring system (0=no pain or pressure, 1=aware of contraction but not painful, 2=aware of pressure or tolerable discomfort, 3=distressing pain or pressure). Measurements were performed every 10 min until analgesia was established (verbal score of 1), and at 30 min and 1 h after the initial dose. Thereafter, 2 hourly VAS were recorded until delivery.

Motor power was assessed using a modified Bromage score 30 min after each top-up and at each request to get out of bed (score 0=no weakness, able to straight leg raise against resistance, 1=not able to straight leg raise, able to flex knee, 2=unable to flex knee, able to flex ankle, 3=unable to move lower limb). If the mother could straight leg raise against resistance she was allowed to get out of bed. Mode of delivery was recorded, as were time intervals between top-ups, duration of first and second stages of labour, and time from insertion of the epidural until delivery. Maternal satisfaction with analgesia was assessed using a VAS, 24 h after delivery.

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Statistical analysis was performed using Minitab 9.2. VAS pain scores for each patient were averaged to give one value, allowing comparison of the overall effect of the analgesic regimens throughout labour. Averaging eliminated differences in the length of labour. The calculation was time-weighted to eliminate bias resulting from shorter time intervals between VAS scores initially as analgesia was being established. A standard time interval of 1 h was used. All VAS were multiplied by the fraction of a 1-h time interval they covered (e.g. 30-min time intervals were multiplied by 0.5 and 2 h intervals by 2.0). These derived values were totalled and divided by the length of labour. Results were analysed using a *t* test for parametric data.

Duration of labour, second stage of labour, time interval from insertion of the epidural until delivery, time interval between top-ups and maternal satisfaction with analgesia were analysed using the Mann–Whitney *U* test. Chi-square test was used to compare mode of delivery between groups.

Visual analogue scores for pain during labour, obtained using a standard technique of on-demand bolus administration of 0.25% plain bupivacaine (measured from other work) have a mean of approximately 20 mm (SD approximately 9 mm). We can assume that if VAS were increased to 30 mm (50% increase), this would be clinically important. To compare the two groups with a power of 0.9 to detect a difference at a significance level of less than 0.05, the sample size required was 35 patients in each group. We studied 40 patients in each group to allow for withdrawals from the study during labour.

Results

Seven women (five in group A, two in group B) were excluded from the study despite good analgesia initially. The threshold for removal was low (women requesting more than two top-ups within 1 h). The length of time in the study before withdrawal for the five women in group A was 2 h 25 min to 7 h 30 min. The two women in group B were withdrawn at 4 h and 4 h 25 min. All five women in group A required 0.5% plain bupivacaine to provide adequate pain relief and all subsequently delivered by Caesarean section because of failure to progress in labour. Both women in group B required fentanyl to relieve rectal pressure. One subsequently had a Caesarean section because of failure to progress and the other instrumental delivery after a long second stage.

For time to first painless contraction, data from all women were used, but for mode of delivery, length of labour and second stage, and time between top-ups, only patients who completed the study were assessed (35 women in group A, 38 in group B). Patient characteristics (age, height, weight, parity and cervical dilatation when epidural was sited) were similar in each group.

Times to first painless contraction (verbal score$\le$1) were similar. After injection of the initial bolus, 10 women recorded painless contractions in group A and 11 in group B by 10 min. By 20 min, another 14 patients in group A and 20 in group B were pain free, and all women reported pain-free contractions by 30 min.

Total VAS for pain throughout labour were similar in both groups (P=0.31; 95% confidence interval (CI) −2.15, 6.63) (table 1). Although the time interval between top-ups was significantly shorter in group A (P=0.0001; 95% CI 10.00, 30.00), women in this group received significantly less bupivacaine (table 1).

In group A, 39 of 40 women were assessed as able to get out of bed and 24 women got out of bed during labour. In group B, eight of 40 women were thought to be able to get out of bed and two got out of bed during labour, but none in group B retained the ability to walk after the first top-up.

Although satisfaction scores for labour were high in both groups, women in group A scored higher (table 1).

The time interval between insertion of the epidural and delivery was similar in both groups and although women in group A had shorter labours, this was not significant (table 2). Duration of the second stage of labour was significantly shorter in group A (P=0.0003; 95% CI −1.17, −0.27) (table 2) and more women in this group had spontaneous vertex delivery (77% compared with 58%) (table 3). There were fewer instrumental deliveries in group A (P=0.03) (table 3). Caesarean section rates were similar.

Table 1 Pain scores (VAS) as weighted-average (mean, SD) (*t* test), time interval between top-ups, total bupivacaine administered during labour, total fentanyl administered during labour and satisfaction with analgesia in labour (VAS) (median, interquartile range) (Mann–Whitney *U* test) in groups A and B. *P* values and 95% confidence intervals (CI) are also given

	Group A	Group B	*P*	95% CI
VAS pain (mm)	20.52 (10.16)	18.29 (9.43)	0.31	(−2.15, 6.63)
Time between top-ups (min)	90 (60–117.5)	110 (82.5–140)	0.0001	(10.00, 30.00)
Total bupivacaine (mg)	45 (35–50)	87.5 (62.5–112.5)	<0.001	(−57.51, −22.50)
Total fentanyl (μg)	110 (90–120)			
Satisfaction with analgesia VAS (mm)	84 (75.75–89.75)	77.5 (72.0–88.0)	0.04	(−0.001, 10.001)

Table 2 Duration of labour, first stage and second stage, and time from insertion of the epidural to delivery (h) (median, interquartile range) (Mann–Whitney *U* test)

	Group A	Group B	*P*	95% CI
Labour	7.33 (5.69–9.87)	8.35 (6.6–11.8)	0.17	(−3.08, 0.50)
1st stage	6.58 (4.96–8.66)	7.17 (5.42–9.5)	0.4	(0.07, 3.16)
2 stage	0.78 (0.33–0.96)	1.5 (0.83–2.5)	0.0003	(−1.17, −0.27)
Epidural to delivery	5.25 (3.5–6.29)	6.2 (4.72–9.17)	0.057	(−2.733, 0.082)

Table 3 Method of delivery (number of women) (chi-square test). SVD=Spontaneous vertex delivery

	Group A (n=35)	Group B (n=38)	P
SVD	27	22	0.08
Instrumental	2	9	0.03
Caesarean section	6	7	0.89

Discussion

We have demonstrated that with an epidural top-up technique using 0.1% bupivacaine with fentanyl 2 µg ml^{-1}, analgesia was similar to that using 0.25% plain bupivacaine, but motor power was retained allowing women to mobilize. There also appear to be beneficial effects on the progress of labour, with a clinically important reduction in the length of the second stage and instrumental delivery rate.

With this technique, 39 of 40 women retained adequate motor power to be judged able to walk and 60% chose to get out of bed during labour. Reduction in motor block allowing independent movement and awareness of contractions without pain has been shown to be popular with mothers.[10] Retention of pelvic floor sensation and motor function may allow appropriate coordinated pushing during the second stage, improving rotation and descent of the fetal head through the pelvis. Epidural local anaesthetic may attenuate endogenous oxytocin production reducing uterine contractility during the second stage.[13 14] The significantly lower dose of bupivacaine required by women in group A may allow better uterine function and explain the shorter second stage of labour and reduced instrumental delivery rates observed in this study. These are important clinical findings because both a long second stage and instrumental delivery have associated morbidity for the mother,[15–17] pose a controversial potential risk to the baby[18–20] and negatively influence maternal satisfaction with the experience of labour.[21] Although epidural analgesia produces excellent analgesia, this does not automatically produce maternal satisfaction with labour, and less effective methods of analgesia have produced higher satisfaction scores.[21] We demonstrated high maternal satisfaction with both epidural solutions, which was significantly greater in the bupivacaine–fentanyl group.

Analgesia was established (verbal score=1) by 30 min in all women. Establishing analgesia with an epidural bolus is effective but takes longer than a combined spinal–epidural technique, which has been described widely.[10] However, it avoids the complications of deliberate dural puncture.[11] The time difference between establishing spinal rather than epidural analgesia should be viewed in the context of the duration of labour and the potential complications of the spinal component of a combined technique.

Comparing the two epidural solutions, we showed that the duration of analgesia provided by each top-up was significantly shorter in group A than in group B (table 1). This influences the management of the epidural with more frequent top-ups and care in recognizing block regression to avoid loss of analgesia. However, the benefits of this solution are evident and PCEA or continuous infusion may prevent this potential problem.

In summary, we have shown that establishing epidural analgesia in labour with 15 ml of 0.1% bupivacaine combined with fentanyl 50 µg, followed by top-ups of 10 ml of 0.1% bupivacaine with 0.0002% fentanyl, produced similar analgesia to that obtained from the same volume of 0.25% bupivacaine alone, but motor block was minimized. This may influence the progress of labour, decreasing the duration of the second stage and incidence of instrumental delivery, and produce high maternal satisfaction with the experience of labour.

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References

1. Li DF, Rees GAD, Rosen M. Continuous extradural infusion of 0.0625% or 0.125% bupivacaine for pain relief in primigravid labour. *British Journal of Anaesthesia* 1985; **57**: 264–270.
2. Murphy JD, Hutchinson K, Bowden MI, Lewis M, Cooper GM. Bupivacaine versus bupivacaine plus fentanyl for epidural analgesia. effect on maternal satisfaction *British Medical Journal* 1991; **302**: 564–567.
3. Thorburn J, Moir DD. Extradural analgesia: the influence of volume and concentration of bupivacaine on mode of delivery, analgesia efficacy, and motor block. *British Journal of Anaesthesia* 1981; **53**: 933–939.
4. Crawford JS. Experiences with epidural morphine in obstetrics. *Anaesthesia* 1981, **36**: 207–209.
5. Husemeyer RP, O'Connor MC, Davenport HT. Failure of epidural morphine to relieve pain in labour. *Anaesthesia* 1980, **35**: 161–163.
6. Vella LM, Willats DG, Knott C, Linton DJ, Justins DM, Reynolds F. Epidural fentanyl in labour: an evaluation of the systemic contribution to analgesia. *Anaesthesia* 1985; **40**: 741–747.
7. McGrady EM, Brownhill DK, Davis AG. Epidural diamorphine and bupivacaine in labour. *Anaesthesia* 1989, **44**. 400–403.
8. Cohen SE, Tan S, Albright GA, Halpern J. Epidural fentanyl/bupivavaine for obstetric analgesia. *Anesthesiology* 1987; **67**: 403–407.
9. Chestnut DH, Laszewski LJ, Pollack KL, Bates JN, Manago NK, Choi WW Continuous epidural infusion of 0.0625% bupivavaine–0.0002% fentanyl during the second stage of labor. *Anesthesiology* 1990; **72**· 613–618.
10. Collis RE, Baxandall ML, Srikantharajah ID, Edge G, Kadim MY, Morgan BM. Combined spinal epidural (CSE) analgesia: technique, management, and outcome of 300 mothers *International Journal of Obstetric Anesthesia* 1994; 3 75–81.
11. Collis RE, Baxandall ML, Srikantharajah ID, Edge G, Kadim MY, Morgan BM. Combined spinal–epidural analgesia with the ability to walk throughout labour. *Lancet* 1993; **341** 767–768.
12. Harding SA, Collis RE, Morgan BM. Meningitis after combined spinal–extradural anaesthesia in obstetrics. *British Journal of Anaesthesia* 1994; **73**: 545–547.
13. Goodfellow CF, Hull MGR, Swaab DF, Dogterom J, Buijs RM. Oxytocin deficiency at delivery with epidural analgesia. *British Journal of Obstetrics and Gynaecology* 1983; **90**: 214–219.
14. Bates RG, Helm CW, Duncan A, Edmonds DK. Uterine activity in the second stage of labour and the effect of epidural analgesia. *British Journal of Obstetrics and Gynaecology* 1985; **85**: 749–755.
15. Sultan AH, Kamm MA, Hudson CN. Pudendal nerve damage during labour: prospective study before and after childbirth. *British Journal of Obstetrics and Gynaecology* 1994; **101**. 22–28.
16. Sultan AH, Kamm MA, Hudson CN, Thomas JM, Bartram CI. Anal-sphincter disruption during vaginal delivery *New England Journal of Medicine* 1993; **329**: 1905–1911.

17. Snooks SJ, Swash M, Henry MM, Setchell M. Risk factors in childbirth causing damage to the pelvic floor innervation. *British Journal of Surgery* 1985; 72: S15–17.
18. Friedman EA, Sachtleben-Murray MR, Dahrouge D, Neff RK. Long term effects of labor and delivery on offspring: A matched-pair analysis. *American Journal of Obstetrics and Gynecology* 1984; **150**: 941–945.
19. Gilstrap LC, Hauth JC, Schiano S, Connor KD. Neonatal acidosis and method of delivery. *Obstetrics and Gynecology* 1984; **63**: 681–685.
20. Dieker LJ, Rosen MG, Thompson K, Lynn P. Midforceps deliveries: Long-term outcome of infants. *American Journal of Obstetrics and Gynecology* 1986; **154**: 764–768.
21. Morgan BM, Bulpitt CJ, Clifton P, Lewis PJ. Analgesia and satisfaction in child birth (The Queen Charlottes 1000 mother survey). *Lancet* 1982; 808–810.

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Local anaesthetic infiltration for surgical exodontia of third molar teeth: a double-blind study comparing bupivacaine infiltration with i.v. ketorolac

D. J. MELLOR, A. H. MELLOR AND E. M. MCATEER

Summary

We studied 40 patients undergoing surgical removal of at least two third molar teeth under general anaesthesia. Patients were allocated randomly to one of two groups: group B (n=20) received bupivacaine up to 2 mg kg^{-1}, infiltrated around the inferior alveolar nerves bilaterally, and group K (n=20) received ketorolac 10 mg i.v. at the start of surgery. There were no significant differences between the two groups in postoperative pain scores measured at 1 h using a visual analogue scale. Group K had a significantly lower incidence of side effects related to intra-oral anaesthesia. Swallowing, speech and oral continence were significantly better. Group K scored higher for overall patient satisfaction, measured using a visual analogue scale. We failed to demonstrate any difference in early postoperative recovery (coughing, laryngospasm, stridor or arterial oxygen desaturation) between the groups. We conclude that the use of 0.5% bupivacaine infiltration was no more effective than a single 10-mg injection of ketorolac while giving rise to a higher rate of "minor" airway complications and lower patient acceptability. (*Br. J. Anaesth.* 1998; **81**: 511–514).

Keywords: anaesthetics local, bupivacaine; surgery, dental; pain, postoperative; non-steroidal anti-inflammatory drugs; analgesics non-opioid, ketorolac

Surgical extraction of impacted upper and lower third molar teeth (wisdom teeth) is a procedure frequently carried out on an outpatient, day-stay basis.[1] However, pain after this procedure is frequently severe[1] and analgesia is necessarily a balance between achieving adequate pain relief while causing minimum side effects, consistent with early discharge.

Several studies have demonstrated the efficacy of opioids,[1] non-steroidal anti-inflammatory agents[2–6] and local anaesthetic infiltration[7–9] in the control of postoperative dental pain. Each approach to postoperative analgesia has its own profile of benefits and side effects. In particular, widespread use of intra-oral local anaesthetics causes difficulty with speech and swallowing and many feel this detracts from its usefulness.[10] Anxiety has been expressed that widespread intra-oral numbness may predispose to upper airway complications in the immediate postoperative period.[10]

The aim of this study was to investigate the efficacy, safety and patient tolerability of the widespread local anaesthesia produced by bilateral inferior dental nerve block compared with i.v. ketorolac.

Patients and methods

The study was approved by the Research Ethics Committee of the United Leeds Teaching Hospitals NHS Trust and all patients gave written consent. We studied 40 patients, aged more than 18 yr, undergoing at least two lower third molar teeth extractions under general anaesthesia. Patients undergoing removal of upper wisdom teeth or other dental surgery were included only if simultaneously undergoing bilateral lower jaw surgery. In addition to fulfilling our institution's criteria for suitability for day-case surgery (body mass index <30 kg m^{-2} and ASA grade I or II) patients were excluded if they had a history of asthma or intolerance to non-steroidal analgesics or local anaesthetic agents.

Patients were allocated randomly to one of two groups by opening sealed envelopes in the anaesthetic room. There were 20 patients in group K (ketorolac) and 20 in group B (bupivacaine). On arrival in the anaesthetic room, electrocardiogram, pulse oximeter and non-invasive arterial pressure monitoring were instituted. After i.v. cannulation, anaesthesia was induced with propofol 2.5 mg kg^{-1} i.v. followed by another 0.5–1 mg kg^{-1} if indicated clinically, fentanyl 1 μg kg^{-1} i.v. and mivacurium 0.2 mg kg^{-1} i.v.

The larynx was intubated using a size 6.5 or 7.0 cuffed nasotracheal tube and anaesthesia was maintained with 1–2% isoflurane and 70% nitrous oxide in oxygen. A water moistened throat pack was inserted by the anaesthetist.

All patients were operated on by the same surgeon (A. H. M.). All local anaesthetic blocks were performed by the surgeon who was experienced in performing third molar extractions under both general and local anaesthesia. Patients in group B received 0.5% bupivacaine i.v. to each side of the jaw, anaesthetizing the inferior dental nerve. In addition, any other surgical areas (upper third molars) were infiltrated with the same solution. A maximum dose of bupivacaine 2 mg kg^{-1} was used. Patients in group K received ketorolac 10 mg i.v. before the start of surgery. Placebo (normal saline) was injected in the

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same manner to the inferior dental nerves and other surgical areas. Inferior dental nerve block was performed bilaterally with the patient's mouth opened with a surgical prop. A 25-gauge needle was inserted just medial to the anterior border of the mandible, inside the mouth, at a point 1 cm above the occlusal surface of the lower third molar. Keeping the syringe parallel to the floor of the mouth and the syringe barrel overlying the premolars of the opposite side, the needle was advanced 2 cm until the mandible was contacted, withdrawn slightly and 2 ml of solution injected.[11] Surgery was performed using a dental burr rather than the lingual split method.[12]

At the end of surgery, the operative time was recorded as the total time from starting to ending administration of isoflurane. In addition, difficulty of surgery was graded I–III for each tooth removed (table 1).

The patient's lungs were ventilated with 100% oxygen until spontaneous recovery from mivacurium neuromuscular block was adequate to extubate the trachea. Extubation was performed in the left lateral, head-down tilt position. It was performed by the blinded observer who was responsible for grading the quality of immediate postoperative recovery. Oxygen was administered by variable performance mask for 10 min after spontaneous eye opening, and the patient was discharged from hospital 2 h after recovery.

Assessments were made of the quality of recovery and analgesia in the immediate postoperative period. Quality of immediate recovery and presence of airway complications in the first 10 min after operation were recorded by the same blinded observer and recorded on a four-point scale. One hour after the end of anaesthesia, pain was assessed using a visual analogue scale from 0–100 mm. At this time, assessment was made of oral continence by observing the patient swilling 30 ml of water in the mouth. Oral continence and coughing were noted and graded. Swallowing was tested next and graded according to the patient's degree of described difficulty. Speech quality was assessed by the same blinded observer who noted the presence or absence of speech slurring when the patient read out a test sentence (a nursery rhyme). Lastly, the patient was asked to grade satisfaction with the whole surgical and anaesthetic experience on a visual analogue scale. The patient was given identical written instructions to combine their experiences of numbness, difficulty in speech and swallowing, and amount of pain into a single satisfaction score. All postoperative assessments were performed by the same anaesthetist who was blinded to the anaesthetic technique used. Blinding was achieved by exclusion of the assessor from the anaesthetizing and operating areas. The rating scale used by the blinded observer is shown in table 3. The visual analogue scoring system was explained to participating patients before anaesthesia.

Table 1 Grade of surgical difficulty in third molar exodontia Graded before operation from radiographs

I=No obvious hard tissue impaction. Tooth likely to elevate without soft-tissue relieving incision.
II=Hard tissue impaction, requiring minimal amount of bone removal.
III=Hard tissue impaction requiring moderate bone removal and tooth division.

Analgesia for all patients comprised codeine phosphate 30 mg–paracetamol 500 mg combination tablets (maximum eight per day). This postoperative analgesic regimen was chosen as we felt it inadvisable to prescribe an oral non-steroidal anti-inflammatory agent without knowing which patients had received ketorolac. Our normal practice is to prescribe ibuprofen.

Statistical analysis of the results was performed using an IBM personal computer with SPSS version 6.1 for Windows. Differences were assessed for significance using Wilcoxon's rank sum test for paired, unmatched data, Student's *t* test for parametric data and Spearman's rank correlation test.

Results

There were 20 patients in each group. There were no significant differences in operative time, operative grade, number of teeth extracted or body weight between the two groups (table 2). Grade of difficulty of extraction of each tooth was recorded and the sum used as an index of surgical trauma.

There was no significant difference in the incidence of airway-related side effects between the groups (table 3) during early recovery from anaesthesia and surgery. However, no patient in group K suffered difficulty with swallowing, speech or oral continence at 1 h compared with 50% of patients in group B ($P<0.005$ for both speech and swallowing and $P<0.01$ for leakage of fluid).

Using the Student's *t* test, there was no significant difference between groups in VAS for pain (table 4).

Table 2 Patient characteristics (mean (SD) or median (range))

	Group K	Group B
Operative time (min)	30.6 (13.5)	31.8 (10.7)
Sum of extraction grade	6 (4–12)	6 (4–12)
No. of teeth extracted	4 (2–6)	4 (2–4)
Patient weight (kg)	70.1 (13.3)	69.2 (9.9)

Table 3 Incidence of local anaesthetic-related side effects

	Group K	Group B
Early recovery airway complications		
1=No untoward events. Saturation >94%	14	12
2=Minor coughing but saturation >94%	4	6
3=Major coughing or laryngospasm with saturation >94%	2	1
4=Any situation leading to desaturation	0	1
Leakage from mouth at 1 h		
1=No leakage	20	11
2=Minor leakage	0	9
3=Major leakage	0	0
4=Coughing	0	0
Difficulty in swallowing water at 1 h		
1=No difficulty	20	10
2=Minor difficulty	0	9
3=Major difficulty	0	1
4=Coughing	0	0
Difficulty in speech at 1 h		
1=Normal speech	20	10
2=Minor slurring noticeable	0	6
3=Major slurring of speech	0	4
4=Difficulty in understanding speech	0	0

Table 4 Visual analogue scores (VAS) for pain and patient satisfaction (mean (SD))

	Group K	Group B
VAS pain (cm)	2.5 (2.4)	3.3 (1.9)
VAS satisfaction (cm)	9.1 (0.72)	7.5 (2.0)

However, the difference in patient satisfaction was significant ($P<0.01$).

When pain and patient satisfaction were correlated with operative time, difficulty of surgery and incidence of side effects, the following correlations were significant ($P<0.01$): duration of surgery correlated positively with pain scores; pain scores correlated inversely with patient satisfaction; and patient satisfaction correlated inversely with incidence of speech impairment and difficulty swallowing. There was no significant correlation ($P<0.01$) between operative difficulty and pain or number of teeth extracted and pain, or between degree of pain and swallowing difficulty.

Discussion

In a recent survey,[13] it was demonstrated that there is a dichotomy in anaesthetic practice for removal of third molar teeth. Half of anaesthetists questioned did not use local anaesthesia as part of their anaesthetic technique. Our aim was to demonstrate the safety, efficacy and tolerability of local anaesthetic when applied as a bilateral nerve block intra-orally.

The safety aspect of intra-oral local anaesthesia is of particular concern to anaesthetists in the period immediately after reversal and emergence from anaesthesia. Any disruption of the protective laryngeal reflexes threatens airway contamination with surgical debris and oral contents. One study[14] concluded that local anaesthetic techniques are safe. However, this series was conducted in patients undergoing surgery with local anaesthesia under conscious sedation with midazolam. Several series of patients have been described who have undergone tonsillectomy under general anaesthesia with local anaesthetic supplementation.[15] This technique does not appear to be associated with an increase in the incidence of early postoperative airway problems and this is in accordance with our findings. We noted no significant increase in postoperative coughing, laryngospasm or stridor between groups. It is impossible from our sample size to conclude that this technique is safe and a report of life-threatening upper airway obstruction after the use of local anaesthesia intra-orally for paediatric tonsillectomy is noted.[16]

The efficacy of local anaesthetic infiltration has been demonstrated previously.[7–10] The fact that it is used widely as the sole form of anaesthesia for third molar exodontia testifies to its effectiveness. However, in our study we failed to demonstrate improved analgesia compared with ketorolac 10 mg i.v. We performed the local anaesthetic blocks while patients were anaesthetized. After operation, we performed no formal testing of the extent of the block. It could be argued that our failure to achieve improved analgesia was a technical problem in that the appropriate nerve bundles were not blocked adequately. However, the high incidence of side effects, such as speech impairment, swallowing difficulties and oral incontinence in group B demonstrated the high "success" rate in achieving neural block. Also, those with a high score for side effects were in no less pain than those with less side effects, suggesting that failure to achieve adequate analgesia was not caused by failure of the nerve blocks. While oral continence and speech impairment do not appear to indicate an inability to protect the patient's airway and could be considered clinically of little relevance, these problems are of major concern to the patient who has difficulty drinking and talking after operation. The correlation between patient satisfaction and incidence of these "minor" side effects is relevant.

Surgery for extraction of third molar teeth is frequently performed under local anaesthesia alone. Clearly, in this respect it is a successful technique. However, surgeons find it difficult to assess intraoperative lingual nerve damage. When used as analgesia for surgery performed under general anaesthesia, the inability to immediately assess nerve damage after operation could be viewed as a further disadvantage of the technique.

The tolerability of local anaesthesia compared with i.v. ketorolac was demonstrated by the highly significant differences in side effects between groups K and B. There were significant differences in patient satisfaction between groups, with increased satisfaction in the ketorolac group. There were no incidences of speech, swallowing or oral continence problems in the ketorolac group compared with more than 50% of patients in the local anaesthesia group. We did not examine specifically problems associated with the use of non-steroidal anti-inflammatory drugs. These agents have a good safety record in outpatient anaesthesia and the highly significant results demonstrated here suggest that the subjective and objective patient tolerability of ketorolac was higher than that of bupivacaine infiltration.

In summary, we have demonstrated no significant difference in analgesia between our two groups. Instead, we demonstrated a significantly higher incidence of "minor" airway-related side effects and a significantly lower level of patient satisfaction in the local anaesthesia group. We failed to demonstrate any increase in early postoperative airway difficulties and, together with other published studies, conclude that the technique is probably safe. Local anaesthetic infiltration may have a place with non-steroidal anti-inflammatory agents, although we have not demonstrated this here. Our study suggests that ketorolac was a better tolerated, equally efficacious agent for sole use.

References

1. Tighe KE, Gillan G, Korczac PKJ, Crossley AWA. An assessment of morphine requirement after wisdom teeth extraction under general anaesthesia. *Anaesthesia* 1995; 50: 816–818.
2. Turner GA, Anson N, Williamson R. A comparison of intramuscular ketorolac with indomethacin suppositories in the treatment of pain after oral surgery. *Anaesthesia and Intensive Care* 1996; 26: 665–668.
3. Wakeling HG, Barry PC, Butler PJ. Postoperative analgesia in dental day case surgery. A comparison between Feldene "melt" (Piroxicam) and diclofenac suppositories. *Anaesthesia* 1996; 51: 784–786.
4. Kiersch TA, Halladay SC, Koschik M. A double-blind, randomised study of naproxen sodium, ibuprofen and placebo in postoperative dental pain. *Clinical Therapeutics* 1993; 15: 845–854.

5. Fricke J, Halladay SC, Bynum L, Francisco CA. Pain relief after dental impaction surgery using ketorolac, hydrocodone plus acetaminophen, or placebo. *Clinical Therapeutics* 1993; **15**: 500–509.
6. Walton GM, Rood JP, Snowdon AT, Rickwood D. Ketorolac and diclofenac for postoperative pain relief following oral surgery. *British Journal of Oral and Maxillofacial Surgery* 1993; **31**: 158–160.
7. Tordoff SG, Brossy M, Rowbotham DJ, James JN, James R, Raphael JH. The effect of pre-incisional infiltration with lignocaine on post-operative pain after molar extraction under general anaesthesia. *Anaesthesia* 1996; **51**: 585–587.
8. Chapman PJ, Ganendran A. Prolonged analgesia following pre-operative bupivacaine neural blockade for oral surgery performed under general anaesthesia. *Journal of Oral and Maxillofacial Surgery* 1987; **45**: 233–235.
9. Wilson IH, Richmond MN, Strike PW. Regional analgesia with bupivacaine in dental analgesia. *British Journal of Anaesthesia* 1986; **58**: 401–405.
10. Tuffin JR, Cunliffe DR, Shaw SR. Do local analgesics injected at the time of third molar removal under general anaesthesia reduce significantly postoperative analgesic requirements? A double blind controlled trial. *British Journal of Oral and Maxillofacial Surgery* 1989; **27**: 27–32.
11. Dobson MB. *Anaesthesia at the District Hospital.* Geneva: World Health Organization, 1988; 95.
12. Absi EG, Shepherd JP. A comparison of morbidity following the removal of lower third molars by the lingual split and surgical burr methods. *International Journal of Oral and Maxillofacial Surgery* 1993; **22**: 149–153.
13. MacKenzie DW, Patel MF. Local anaesthesia for pain relief following wisdom teeth extraction under general anaesthesia. *Anaesthesia* 1996; **51**: 200–201.
14. Holland IS, Stassen LF. Bilateral block: is it safe and more efficient during removal of third molars? *British Journal of Oral and Maxillofacial Surgery* 1996; **34**: 243–247.
15. Johansen M, Harbo G, Illum P. Preincisional infiltration with bupivacaine in tonsillectomy. *Archives of Otolaryngology* 1996; **122**: 261–263.
16. Bean-Lijewski JD. Glossopharyngeal nerve block for pain relief after pediatric tonsillectomy: retrospective analysis and two cases of life-threatening upper airway obstruction from an interrupted trial. *Anesthesia and Analgesia* 1997; **84**: 1232–1233.

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Differential onset of median nerve block: randomized, double-blind comparison of mepivacaine and bupivacaine in healthy volunteers†

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Summary

We have compared the delay in onset of 1% mepivacaine and 0.33% bupivacaine in different nerve fibre types in 10 volunteers undergoing median nerve blocks, in a randomized, double-blind, crossover study. Hot, cold, pinprick and light touch sensations, compound motor action potentials (CMAP), sensory nerve action potentials (SNAP) and skin temperature were recorded at 2-min intervals. Hot, cold, pinprick, light touch sensations, SNAP and CMAP were significantly inhibited, and skin temperature was significantly increased after administration of both agents. The first noticeable reduction in cold sensation was detected later after bupivacaine compared with mepivacaine, but after a delay similar to that of other nerve functions. Bupivacaine and mepivacaine inhibited SNAP and CMAP with a similar time delay to steady-state. Bupivacaine produced steady-state inhibition of hot and cold sensations significantly later than mepivacaine; nevertheless, the sequence that sensory modalities failed, with few exceptions, and the extent of anaesthesia at 40 min were similar for both agents. Our technique provides a novel, multi-modal method of comparing local anaesthetics and related agents over time. (*Br. J. Anaesth.* 1998; **81**: 515–521)

Keywords: nerve, differential block, nerve, transmission, anaesthetics local, bupivacaine; anaesthetics local, mepivacaine, anaesthetic techniques, regional

In clinical practice, bupivacaine appears to have a slower onset of action than mepivacaine, but bupivacaine is thought to inhibit sensory nerve fibres more selectively than mepivacaine.[1] We hypothesized that these differences in nerve blocking characteristics of bupivacaine and mepivacaine could be measured during onset of block with local anaesthetic solutions used in clinical practice, even though these solutions would be expected to produce similar anaesthetic conditions at steady-state. We tested this hypothesis using median nerve blocks as a model system for clinical regional anaesthesia. We chose to study clinical drug concentrations, greatly reducing the possibility that we would detect steady-state differences between sensory modalities or between sensory nerve inhibition, motor nerve inhibition and skin temperature, such as might be observed with lesser degrees of nerve inhibition. That is we did not design our experiment to produce differential block at steady-state and we anticipated inhibition of all modalities.

We assessed speed of onset of inhibition (over 40 min) of median nerve fibre transmission using both objective and subjective data, as in previous studies.[2,3] We obtained objective data (compound motor action potentials (CMAP), sensory nerve action potentials (SNAP) and skin temperature) using standard electrodiagnostic techniques which are particularly useful for comparing inhibition of large myelinated motor and sensory nerve fibres. As SNAP (and CMAP) are composed of summated signals from thousands of axons, specific alteration of one sensory modality could conceivably occur without measurable decrement in SNAP amplitude. In particular, sensory modalities mediated by smaller myelinated or unmyelinated nerve fibres can be inhibited without alteration in SNAP, which measure predominately large (Aα) fibre activity.[4] Therefore, we also used somesthetic testing, the most practical means by which to measure local anaesthetic effects on specific sensory modalities in humans. We assessed subjective perception of cold, hot and pinprick by comparing the same stimulus applied to anaesthetized and unanaesthetized skin, and documenting the persistence of sensation after anaesthesia as a percentage of sensation in unanaesthetized skin. The validity of this "self-reporting" technique has been documented previously.[5,6] Light-touch sensibility was quantitated in anaesthetized skin with von Frey hairs, which yield an explicit measurement of the threshold force stimulus for perception of light touch.[7]

Subjects and methods

Our study was approved by the Clinical Research Practices Committee. After obtaining informed consent, we studied 10 volunteers (nine females) for sequential median nerve blocks, and electrodiagnostic and sensory testing. No volunteer had clinical or electrodiagnostic findings consistent with median nerve dysfunction. Median age of the population was

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32 (range 22–38) yr. Median nerves in dominant and non-dominant hands were studied in either order. Only one drug was injected at each wrist; the two drugs were never studied simultaneously. Bupivacaine and mepivacaine were injected in a random, blinded, crossover manner. The first drug to be studied was selected by the flip of a coin. The first wrist to be injected was selected based on the direction in which the volunteer lay on the examination table. Seven specific assessments were performed before and after injection of mepivacaine or bupivacaine.

Objective measurements included CMAP, SNAP, light touch sensibility and skin temperature. A Nicolet (Madison, WI) Viking electrodiagnostic instrument was used to assess Aα sensory and motor fibres using orthodromic CMAP and antidromic SNAP.[8] Supramaximal (more than 150% of the stimulus which produced maximal SNAP and CMAP amplitudes) electrical stimulation of the median nerve 2 cm proximal to the site of injection of local anaesthetic simultaneously elicited CMAP and SNAP. Belly tendon surface electrodes recorded CMAP from the abductor pollicis brevis muscle; ring electrodes at the base and distal end of the middle finger recorded SNAP. Amplitudes (measured from baseline to peak of the signal) of CMAP and SNAP are reported as percentage of baseline values measured before injection of local anaesthetic. Unmyelinated C-fibre function was monitored measuring skin temperature at the distal end of the index finger with a thermistor accurate to 0.1°C.

Subjective measurements included self-reporting of the perceived intensity of standard hot, cold and pinprick stimuli. Light touch, pinprick, and hot and cold sensations were tested on the proximal palmar surface of the third digit and compared with the same stimulus applied on the volar aspect of the ipsilateral forearm, halfway between the wrist and elbow. These two test sites were marked so that constant regions of skin were tested. Light touch sensibility was assessed using von Frey hair monofilaments (Stoelting Inc., Evanston, IL, USA), which deliver no more than a defined force before bending.[2 7] We confirmed that our von Frey hairs were appropriately calibrated by measuring the force required to bend the monofilaments on a laboratory balance. Pinprick sensation was tested using an opened 2-cm safety pin with its point into the skin just sufficiently to cause visible indentation. Hot and cold sensations were assessed using a 1×1 cm aluminum bar either cooled to a constant temperature of 5–7°C or heated to a constant temperature of 49–52°C. Temperatures were maintained by water baths and remained constant during each experiment. Hot and cold sensations were recorded as a percentage of the sensation perceived in unanaesthetized forearm skin.

After baseline data for all modalities were recorded, the wrist was cleansed with isopropyl alcohol. Median nerve block was performed by inserting a 22-gauge needle just lateral to the palmaris longus tendon and through the flexor retinaculum. We performed our median nerve blocks without using an electrical nerve stimulator and we deliberately avoided producing paraesthesia. Thus it could be argued that we injected our local anaesthetic solutions at an unknown and variable distance from the median nerve. Nevertheless, our technique has produced consistent, successful anaesthesia in this and previous studies.[2 3 5] Bupivacaine 0.33% or 1% mepivacaine 5 ml (both from Astra Pharmaceuticals, Westborough, MA, USA) were injected over 30–45 s. The bupivacaine solutions were formulated by diluting 0.5% bupivacaine with sterile 0.9% saline (Abbott Laboratories, Chicago, IL, USA). These concentrations were judged to be equally efficacious based on widespread clinical use and on unpublished pilot studies in amphibian peripheral nerve.[9 10] Equal efficacy was sought, as speed of onset is greater with more concentrated local anaesthetic solutions. Thus onset of anaesthesia is faster after injections of a solution which yield complete anaesthesia at steady-state compared with a less concentrated solution. A meaningful comparison between two compounds would require that they are presented in concentrations which would yield a similar extent of block at steady-state (equivalent efficacy). All assessments were performed every 2 min over 40 min.

In a power analysis before collecting our data, we assumed that there would be a mean difference of 10 min between bupivacaine and mepivacaine in the time delay until steady-state effects after hot, cold and pinprick sensations were achieved. We assumed an SD of 10 min, β=0.90 and α=0.05. Using paired data to test (one-sided) if mepivacaine was faster than bupivacaine, we estimated that nine volunteers would be needed.

Data are presented as median (confidence intervals). Non-parametric statistical tests were used throughout as our subjects often became insensible to light touch (with von Frey hairs), even with our maximal stimulus, and parametric tests cannot function with "infinite" values. Although many of our assessment techniques produced data that did not deviate significantly from a Gaussian distribution, data from other assessment techniques were clearly not normally distributed. For consistency, we elected not to use parametric techniques for some and non-parametric for others. The presence of a monotonic drug effect over time was indicated when significant Spearman's rank correlations were found between change in measurement and experimental time (measured from the time of drug injection). Data were compared between drugs using four measures: (1) time delay from drug injection until measurement declined or increased to within 10% of the steady-state measurement (values recorded 40 min after injection of local anaesthetic were assumed to be steady-state measurements as nearly every measurement had reached its nadir or zenith well before this time); (2) time delay after drug injection until the first noticeable differences were recorded (only for sensory modalities where subjective responses were recorded); (3) drug effect measured at 40 min; and (4) median drug effect during the course of the experiment using the area under the drug effect *vs* time curve. The latter comparison is analogous to a repeated measures analysis of variance, but for non-parametric data. Using this technique, anaesthetics which produced greater inhibition of hot, cold, pinprick, SNAP or CMAP had *less* area under the effect *vs* time curve; anaesthetics which produced greater inhibition of light touch had *greater* area under the effect *vs* time curve. Changes in skin temperature were not assessed using this technique as skin temperature usually declined before increasing (as discussed above), making any calculation of effect–time area uninterpretable.

Electrophysiological data were reported as percentage of baseline amplitude. Light touch was reported as absolute threshold (measured in mN). Paired Fisher's sign test was used to compare drug effects, using one-sided tests for onset differences between drugs (testing our hypothesis that mepivacaine was faster) and two-sided tests for comparing steady-state drug effects (as our null hypothesis was that the two drug concentrations were equipotent at steady-state). Paired Fisher's sign test was also used to compare the two local anaesthetics at steady-state, using sensory failure (inability to sense hot, cold, pinprick or light touch) as our test criterion. No corrections were made to *P* values; however, to account for multiple comparisons, we arbitrarily assigned $P<0.025$ as our threshold for statistical significance.

Results

Data were collected after injection of both bupivacaine and mepivacaine in all 10 volunteers. In the study population as a whole, median perceived intensity of cold, hot and pinprick sensations declined significantly ($P<0.001$) over time after both bupivacaine and mepivacaine (fig. 1). Each volunteer showed significant declines in cold, hot and pinprick sensations except for one individual ($P=0.10$ after mepivacaine but $P=0.02$ after bupivacaine for hot sensation). Repeated presentation of the same stimulus could lead to accommodation and a decrease in perceived intensity. Nevertheless, our subjects identified no consistent alteration in stimulus intensity in unanaesthetized skin. Bupivacaine and mepivacaine significantly increased the threshold stimulus for perception of light touch, both overall ($P<0.001$ for all subjects together) and for each subject individually (fig. 2). SNAP and CMAP declined significantly ($P<0.001$) after bupivacaine and mepivacaine, both for all subjects and for each volunteer individually (fig. 3).

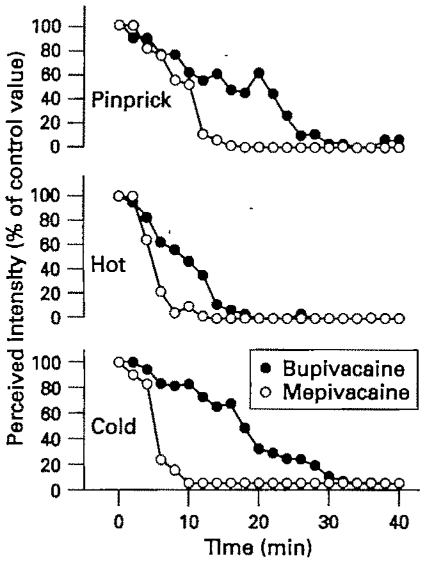

Figure 1 Effects of mepivacaine and bupivacaine on perception of pinprick, hot and cold. Subjects described the intensity of stimuli in anaesthetized skin as a percentage of perceived intensity in a constant region of unanaesthetized skin. Initially, perceived intensity was the same at the two sites, which was recorded as 100%. Bupivacaine had a significantly slower onset of inhibition for hot, pinprick and cold sensibility than mepivacaine. All data are reported as medians.

Both drugs significantly increased skin temperature ($P<0.001$). Skin temperature usually declined immediately, but only briefly, after local anaesthetic injection (fig. 4).

During onset of anaesthesia, there was no significant difference between the two agents in the time delay until a first noticeable decline in pinprick, hot and light touch sensations was detected by our volunteers (table 1). In contrast, a change in cold sensation was detected a median 2 min later after bupivacaine than after mepivacaine, and this difference was statistically significant ($P=0.008$).

The two drugs achieved maximal inhibition of light touch sensation after similar time delays following injection (table 2, fig. 2). In contrast with the other modalities, skin temperature had not

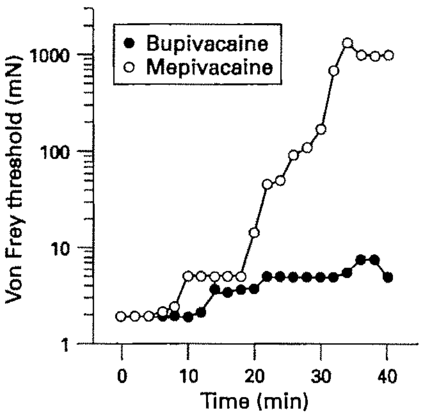

Figure 2 Effects of mepivacaine and bupivacaine on threshold for light-touch sensation assessed using von Frey hairs. The threshold increased significantly after both agents. After mepivacaine, five of 10 subjects had complete loss of light-touch sensation, whereas none of 10 subjects lost light-touch sensation after bupivacaine ($P=0.01$, Fisher's exact test). Data are reported as median threshold for light touch.

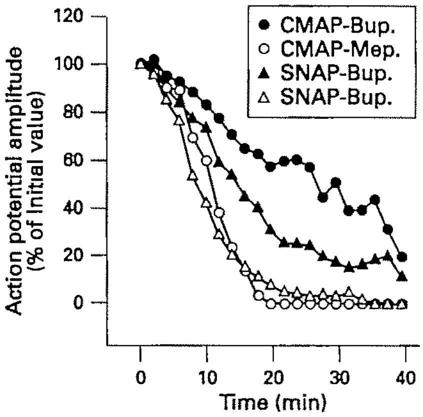

Figure 3 Effects of bupivacaine (Bup.) and mepivacaine (Mep) on sensory nerve action potentials (SNAP) and compound motor action potentials (CMAP). Data are presented as percentage of the initial amplitude of the orthodromic action potential waveform elicited by supramaximal stimulation of the median nerve. Mepivacaine depressed CMAP marginally faster than bupivacaine. At steady-state, inhibition was similar after the two agents. There were no significant differences between the agents in inhibition of SNAP. All data are presented as median values.

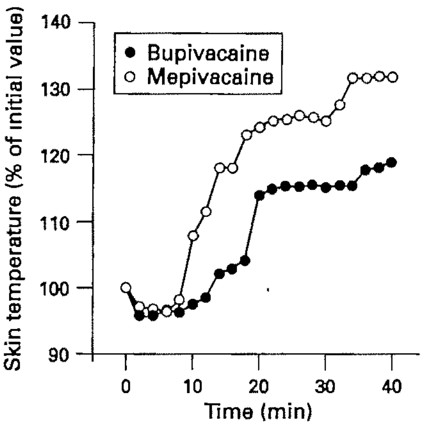

Figure 4 Effects of mepivacaine and bupivacaine on skin temperature. Data are presented as absolute temperature change (°C) compared with baseline measurements. Differences between bupivacaine and mepivacaine were not significant. Consistent with our experience with lidocaine, most subjects demonstrated an initial decline in skin temperature, presumably from a sympathetic response to pain on injection, before demonstrating an increase in skin temperature as a result of presumed C-fibre (or preganglionic B fibre) inhibition and vasodilatation. Data are reported as median values.

always reached its zenith by the 40-min measurement (fig. 4) after injection of either mepivacaine or bupivacaine. Steady-state inhibition of hot and cold sensation was observed significantly later after bupivacaine than after mepivacaine (table 2, fig. 1).

The rate and extent of inhibition by bupivacaine and mepivacaine were also evaluated by comparing the area under the effect *vs* time curve (table 3). Pinprick, cold and light touch sensations showed significantly less inhibition after bupivacaine compared with mepivacaine.

Drug effects measured at 40 min were also compared. In general, there were no significant differences between the agents at 40 min (steady-state). After bupivacaine, the threshold approached the maximal value for light touch in only one volunteer (von Frey hair technique), and no subject lost the ability to sense light touch. After mepivacaine, the threshold for light touch sensation increased above the maximal value (von Frey hair technique) in five of 10 volunteers (P=0.01, Fisher's exact test). Nevertheless, median steady state light touch thresholds were not significantly different between the two local anaesthetics (fig. 2).

The rate and extent of inhibition of the various sensory modalities and electrodiagnostic tests produced by bupivacaine and mepivacaine were also compared using the area under the effect *vs* time curve (table 4). Using this technique, pinprick sensation was inhibited significantly less than hot sensation after bupivacaine and mepivacaine. Hot sensation was inhibited to a significantly greater extent than SNAP and CMAP after both agents, and to a greater extent than cold after bupivacaine. Cold sensation was inhibited to a significantly greater extent than SNAP and CMAP after mepivacaine but not after bupivacaine. No other comparisons approached statistical significance. We did not compare light touch sensation or skin temperature with other modalities because our measurements of the former (in contrast with the other modalities) increased over time. Measurements of the latter were not monotonic and also demonstrated increased values at the 40-min measurement relative to starting measurements.

Table 1 Comparison of mepivacaine with bupivacaine on median latency of first noticeable difference in sensation. All data are presented as median time delay. P values were calculated for one-way Fisher's sign test (to test if mepivacaine produced a "just noticeable" difference sooner than bupivacaine). Differences were calculated using paired data from each subject, subtracting the time delay after mepivacaine from the time delay after bupivacaine

	Mepivacaine		Bupivacaine		Median difference		
Modality	(median)	(range)	(median)	(range)	(median)	(range)	P
Pinprick	4	(2, 10)	2	(2, 10)	–2	(–8, 8)	0.25
Hot	4	(2, 6)	2	(2, 8)	0	(–2, 4)	0.66
Cold	2	(2, 4)	4	(2, 20)	2	(–18, 0)	0.008
Light touch	7	(2, 14)	5	(2, 32)	1	(–6, 26)	0.5

Table 2 Comparison of mepivacaine with bupivacaine on median time delay until steady-state inhibition measured. All data are presented as median. P values were calculated for one-way Fisher's sign test (to test if mepivacaine achieved steady-state inhibition sooner than bupivacaine). Differences were calculated using paired data from each subject, subtracting the time delay after mepivacaine from the time delay after bupivacaine. SNAP=sensory nerve action potentials; CMAP=compound motor action potentials; Skin temp.=skin temperature

	Mepivacaine		Bupivacaine		Median difference		
Modality	(median)	(range)	(median)	(range)	(median)	(range)	P
Pinprick	14	(4, 36)	22	(14, 40)	9	(–6, 28)	0.055
Hot	11	(2, 34)	18	(4, 38)	11	(–22, 24)	0.020
Cold	9	(2, 36)	26	(8, 40)	11	(0, 32)	0.020
Light touch	30	(10, 40)	31	(2, 40)	–2	(–30, 30)	0.500
SNAP	26	(10, 40)	33	(18, 40)	8	(–22, 20)	0.410
CMAP	19	(6, 38)	35	(20, 40)	14	(–18, 24)	0.055
Skin temp.	38	(0, 40)	38	(0, 40)	2	(–40, 20)	0.140

Table 3 Comparison of mepivacaine with bupivacaine on overall drug effect compared using area under effect *vs* time curve All data are presented as median (in effect–time area). Effect–time area was calculated using percentage of baseline (unanaesthetized) values as the effect for pinprick, hot, cold, SNAP and CMAP. The light touch effect was recorded as threshold force (mN). Less area denotes a greater reduction in pinprick, hot, cold, SNAP or CMAP. Greater area denotes greater inhibition of light touch. *P* values calculated for two-way Fisher's sign test. Differences were calculated using paired data from each subject subtracting mepivacaine effect–time area from bupivacaine effect–time area. SNAP=Sensory nerve action potentials; CMAP=compound motor action potentials

	Mepivacaine		Bupivacaine		Median difference		
Modality	(median)	(range)	(median)	(range)	(median)	(range)	*P*
Pinprick	955	(238, 2705)	1902	(629, 3661)	795	(–726, 2267)	0.022
Hot	599	(190, 1937)	1086	(254, 3384)	482	(–1040, 2199)	0.11
Cold	662	(206, 2210)	1825	(658, 3125)	1033	(–146, 2106)	0.022
Light touch	186	(141, 240)	143	(121, 178)	–37.5	(–86, 11)	0 022
SNAP	1130	(500, 3328)	1820	(1067, 3629)	779	(–2210, 2077)	0.34
CMAP	1152	(299, 3192)	2330	(860, 4140)	1567	(–1636, 3620)	0.34

Table 4 Comparisons of median overall drug effects measured as area under the effect *vs* time curves (% min) SNAP=Sensory nerve action potentials; CMAP=compound motor action potentials. All data are presented as medians (first modality–second modality) in units of % min. Statistical comparisons were performed using paired data from each subject. A positive value indicates that the first modality was inhibited less than the second modality over the course of the experiment

	Mepivacaine			Bupivacaine		
Comparison	(median)	(range)	*P*	(median)	(range)	*P*
Pinprick *vs* hot	218.4	(29, 790)	0.002	380	(95, 2050)	0.002
Pinprick *vs* cold	229.3	(–341, 822)	0.34	89.8	(–1192, 884)	0.75
Pinprick *vs* SNAP	–190	(–2379, 467)	1.0	–184	(–1916, 1830)	0.75
Pinprick *vs* CMAP	–23.8	(–2954, 535)	0.75	–714	(–2784, 1974)	0.11
Hot *vs* cold	–53.6	(–569, 155)	1.0	–328	(–1625, 492)	0.021
Hot *vs* SNAP	–567	(–2408, 258)	0.021	–593	(–2363, 1235)	0.021
Hot *vs* CMAP	–469	(–3001, -32)	0.002	–1031	(–2885, 1587)	0.021
Cold *vs* SNAP	–655	(–2270, 407)	0.022	–174.7	(–1724, 946)	0.75
Cold *vs* CMAP	–296.3	(–2754, 76)	0.022	–638	(–2793, 1803)	0.34
SNAP *vs* CMAP	35.2	(–2023, 2346)	1.0	–289.4	(–2790, 2049)	0.75

Discussion

Our data have demonstrated that during onset of median nerve block, 0.33% bupivacaine inhibited sensations of cold and hot significantly more slowly compared with 1% mepivacaine. A "just noticeable" difference in cold sensation was detected significantly later with bupivacaine than with mepivacaine. In contrast, at the 40-min assessment, there were no significant differences between the agents for inhibition of SNAP and CMAP. While mepivacaine generally has a faster onset of median nerve block than bupivacaine, the various sensory modalities and nerve fibre types responded in different ways. Some measurements consistently had greater overall inhibition than others. Hot sensation was inhibited to a greater overall extent than pinprick sensation, SNAP or CMAP, consistent with a faster onset (table 4). Thus the clinician can expect to receive earlier signs of nascent median block from either bupivacaine or mepivacaine by testing with a hot stimulus than by using pinprick. Curiously, hot sensation was inhibited significantly faster than cold sensation after bupivacaine but not after mepivacaine. The relatively faster onset of inhibition of cold sensation after mepivacaine (compared with bupivacaine) resulted in significant differences in onset between cold and SNAP and CMAP with mepivacaine, but not with bupivacaine. In contrast, the clinician is less likely to be surprised by incomplete anaesthesia if loss of pinprick sensation or the signals from electrodiagnostic tests (SNAP and CMAP) are used as criteria for satisfactory anaesthesia, rather than a thermal stimulus. We also noted that our techniques provided a novel means by which responses to local anaesthetics and other peripheral-acting analgesic agents may be compared over time.

Whereas differential block of nerve fibres *in vitro* has been shown to occur (using electrophysiological measurements) with constant (submaximal) concentrations of local anaesthetics (at steady-state), we found limited evidence for differential block after 40 min of exposure to clinical drug concentrations (when local anaesthetic binding to Na channels should have reached a maximum).[11 12] Indeed, as expected, we identified few differences between bupivacaine and mepivacaine at 40 min. Bupivacaine 0.33% and 1% mepivacaine produced profound inhibition after 40 min.

Our technique, which included testing of multiple sensory modalities, action potentials from sensory and motor systems, and skin temperature, allowed detection of subtle differences in the extent of conduction block of different fibres. Nevertheless, it has many limitations. We did not objectively measure intra-subject variability, that is the consistency with which each volunteer graded onset of block. Such comparisons have been performed previously.[6] We have previously documented measurements after median nerve block with 0.9% saline, confirming the ability of volunteers to detect no significant alteration in the perceived intensity of constant sensory stimuli.[5] Sensory thresholds may vary dramatically over small regions of skin.[13] To overcome this potential variability, we marked the skin and presented the stimuli to the same location each time.

We recognize that in many cases we have not measured the time of sensory or motor nerve failure, but measured decrements in nerve fibre function over time. Thus our conclusions regarding onset (where we used the time delay until steady-state conditions were obtained) may differ from those of other authors who may have taken onset of local anaesthesia as complete insensibility. We also recognize that each peripheral nerve may have its own organizational characteristics, and may carry different fibre types. Thus we cannot exclude the possibility that different results may have been obtained had we tested mepivacaine and bupivacaine on a different peripheral nerve. Such comparisons are planned.

We recognize that some measurements, notably skin temperature, may not have reached steady-state values by 40 min. In these cases, estimates of median time delay to achieve steady-state drug effects must be interpreted cautiously. We found a similar onset of increase in skin temperature after mepivacaine and bupivacaine, possibly because bupivacaine has a predilection for inhibiting unmyelinated vasomotor C fibres (or preganglionic B fibres), as onset of bupivacaine anaesthesia was slower for most other modalities. Alternatively, delay between sympathetic nerve block and an increase in skin temperature could obscure differences between mepivacaine and bupivacaine. Data recording longer than 40 min may be required to detect a difference between these agents. Finally, skin temperature usually declined immediately, but only briefly, after injection of local anaesthetic, probably as a result of pain- and anxiety-induced peripheral vasoconstriction, making assessment of onset times for an increase in skin temperature more difficult to define.

We believe that mepivacaine and bupivacaine concentrations used in this study were nearly equipotent for clinical nerve blocks and our results at 40 min support that belief. Most studies comparing the clinical effects of mepivacaine and bupivacaine have found relative potency ratios (using drug concentrations measured in $mg\ dl^{-1}$) of 1:3–1:4.[9, 14–16] Similar molar potency ratios have been observed in studies of local anaesthetics applied to isolated nerves.[10] Thus using these data as our guide, as a worst case, the mepivacaine solution used in this study should have been equivalent or slightly less potent than the bupivacaine solution. Careful comparison of sub-blocking concentrations of the various local anaesthetics using our measurement techniques could yield accurate and precise concentration equivalency data in humans, data which are at present lacking. We recognize that speed of onset of local anaesthesia is related to the dose of local anaesthetic and that miscalculation of the relative potency of mepivacaine and bupivacaine could confound comparison between them regarding relative rates of onset.

Our data suggest that a decline in perceived intensity of heat is the earliest subjective test identifying onset of median nerve block. Other studies have found that temperature sensation is impaired early during nerve blocks (for review, see Raymond and Gissen[1]). We also found that the nerve fibres subserving sensations of hot and cold ($A\text{-}\partial$ and C-fibres) were inhibited more rapidly by local anaesthetics than fibres responsible for pinprick sensation ($A\partial$ fibres).[1] These findings are at variance with the *in vitro* work of Gissen and colleagues, who found that C fibres were more resistant to local anaesthesia than $A\alpha$ fibres.[11, 12, 14] Gissen and colleagues performed their studies at steady-state in isolated rabbit vagus nerves; thus differences between their data and ours could result from species differences or from differences in the internal architecture between cranial (vagus) and peripheral (median) nerves. Differential onset of anaesthesia could have different underlying mechanisms than differential block at steady-state.

A decline in hot or cold sensation may not provide a reliable test for adequacy (completeness) of neural block for surgical incision. Although surgical anaesthesia can be obtained without complete motor block, the presence of motor block substantially increases the likelihood that adequate sensory anaesthesia is also present after either local anaesthetic, as loss of CMAP amplitude did not precede loss of sensory modality. Clinicians generally do not have the capability of monitoring CMAP, and we caution that other tests of motor block may not yield identical results.

We conclude that 1% mepivacaine generally produced more rapid onset of anaesthesia than 0.33% bupivacaine. Of potential clinical importance was that thermal sensation appeared more susceptible to block than other modalities after both agents. Testing for small fibre block using a warm stimulus may provide an overly sanguine assessment of inhibition of larger sensory and motor nerve fibres, particularly during onset of anaesthesia. Therefore, we advise caution if clinicians choose tests of small fibre function (hot or cold sensation) to determine if regional block is adequate for surgical incision. Further study is required to determine if the characteristics of median block which we observed can be extrapolated to other local anaesthetics, other nerves, or spinal or epidural anaesthesia. But we predict that our measurement techniques may prove useful to define precisely differences between local anaesthetics with regard to potency and differential block of sensory modalities during clinical regional anaesthesia. Our technique is particularly useful as longer-persisting agents which produce selective analgesia become available for treatment of acute and chronic pain.

References

1. Raymond SA, Gissen AJ. Mechanisms of differential nerve block. In: Strichartz GR, ed. *Handbook of Experimental Pharmacology: Local Anesthetics*. New York: Springer-Verlag, 1987; 95–164.
2. Butterworth JF, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. *Anesthesiology* 1990; **72**: 962–965.
3. Butterworth JF, Walker FO, Neal JM. Cooling potentiates lidocaine inhibition of median nerve sensory fibers. *Anesthesia and Analgesia* 1990; **70**: 507–511.
4. Jamal GA, Hansen S, Weir AI, Ballantyne JP. The neurophysiologic investigation of small fiber neuropathies. *Muscle and Nerve* 1987; **10**: 537–545.
5. Flanagan MT, Walker FO, Butterworth JF IV. Failure of

meperidine to anesthetize human median nerve: a blinded comparison with lidocaine and saline. *Regional Anesthesia* 1997; 22: 73–79.

6. Stevens SS. Neural events and the psychophysiologic law. *Science* 1970, 170: 1043–1050.
7. Head H. Methods of examining sensation. In: Head H, ed. *Studies in Neurology.* London: Frowde, 1920; 12–34.
8. Kimura J. *Electrodiagnosis in Diseases of Nerve and Muscle. Principles and Practice.* Philadelphia: FA Davis, 1983.
9. Covino BG, Vassallo HG. Clinical aspects of local anesthesia. In: Covino BG, Vassallo HG, eds. *Local Anesthetics: Mechanisms of Action and Clinical Use.* New York: Grune and Stratton, 1976; 57–94.
10. Covino BG, Vassallo HG. Chemical aspects of local anesthetic agents. In: Covino BG, Vassallo HG, eds *Local Anesthetics: Mechanisms of Action and Clinical Use.* New York: Grune and Stratton, 1976; 1–11.
11. Gissen AJ, Covino BG, Gregus J. Differential sensitivities of mammalian nerve fibers to local anesthetic agents. *Anesthesiology* 1980; **53**: 467–474.
12. Wildsmith JAW, Gissen AJ, Gregus J, Covino BG. The differential nerve blocking activity of amino-ester local anaesthetics. *British Journal of Anaesthesia* 1985; 57: 612–620.
13. Dallenbach KM. The temperature spots and end-organs. *American Journal of Physiology* 1927; 39: 402–427.
14. Wildsmith JA, Gissen AJ, Takman B, Covino BG. Differential nerve blockade: esters *vs* amides and the influence of pKa. *British Journal of Anaesthesia* 1987; 59: 379–384
15. Reynolds F, Bryson TH, Nicholas AD. Intradermal study of a new local anaesthetic agent: aptocaine. *British Journal of Anaesthesia* 1976; 48: 347–354.
16. Lofstrom JB. Ulnar nerve blockade for the evaluation of local anaesthetic agents. *British Journal of Anaesthesia* 1975; 47: 297–300.

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Effect of anxiety on the rate of gastric emptying of liquids

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Summary

The efficacy of preoperative fasting is reduced in the presence of any factor which delays gastric emptying. We examined the association between anxiety and gastric emptying in adult patients undergoing elective surgery. Immediately before operation, 21 patients completed both a Spielberger state trait inventory (used to quantify current anxiety state (STAI$_s$) and anxiety predisposition (STAI$_t$)), and the Amsterdam preoperative anxiety and information scale (used to quantify anxiety and need for information). Gastric emptying was measured using the paracetamol absorption technique. Four to 10 weeks later, gastric emptying and STAI were measured again. Patients were more anxious before than after operation (STAI$_s$=mean 35.4 (SD 10.9) and 25 (4.1), respectively; P=0.0004). Neither anxiety state (P=0.40) nor measures of anxiety relative to anxiety predisposition (P=0.86) influenced gastric emptying (as measured by area under the paracetamol absorption–time curve). This contrasts with previous findings that anxiety in patients with low anxiety predisposition scores delays gastric emptying. (*Br. J. Anaesth.* 1998; **81**: 522–525).

Keywords: psychological responses; gastrointestinal tract, emptying

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Traditionally, patients undergoing elective surgical procedures have been required to fast for at least 6 h before general anaesthesia.[1–4] The rationale for this practice is that this fasting period allows enough time for gastric emptying to occur, thus diminishing the risk of pulmonary aspiration of gastric contents. The effectiveness of the fasting period is reduced in the presence of any factor which inhibits gastric emptying.

It is commonly held that "stress" or "anxiety" delays gastric emptying.[1] In the preoperative period, using the Spielberger state trait inventory (used to quantify current anxiety state (STAI$_s$)) scale and a threshold score of 46 for significant anxiety, the prevalence of anxiety in an adult European group of preoperative patients (n=200) was 32%.[5] To date, the effect of anxiety on gastric emptying during the preoperative period has not been studied adequately. Nygren and colleagues,[6] in a small study, used a visual analogue scale to quantify anxiety in patients who drank either 400 ml of water (n=6) or a carbohydrate-rich drink (n=6) before operation. Patient position was not standardized. They concluded that anxiety did not influence the rate of gastric emptying.

We undertook to formally quantify anxiety using the previously validated Spielberger state trait anxiety inventory (STAI)[7] and the Amsterdam preoperative anxiety and information scale (APAIS),[5] before estimation of gastric emptying of liquids using the paracetamol absorption technique.[8]

Patients and methods

After obtaining approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals, and written informed consent, we studied 21 fasting ASA I or II patients who completed the STAI on the morning of surgery. This evaluated both current anxiety state (STAI$_s$) and personality traits predisposing to anxiety (STAI$_t$). Patients received a numerical score, ranging from 20 to 80, for both STAI$_s$ and STAI$_t$. The numerical difference between STAI$_s$ and STAI$_t$ (STAI$_{s-t}$) is taken as a measure of the extent to which the individual's current anxiety state differs from his baseline anxiety predisposition.[9] Patients then completed the APAIS, a six-item questionnaire designed to measure anxiety and need for information in preoperative patients. Patients received a numerical score for anxiety (APAIS$_{anx}$) ranging from 4 to 20, and an information requirement score (APAIS$_{inf}$) ranging from 2 to 10. The sum of APAIS$_{anx}$ and APAIS$_{inf}$ is the total APAIS score, APAIS$_{tot}$.

Gastric emptying was measured using a paracetamol absorption technique.[8] Patients fasted for at least 8 h before the study. An i.v. cannula was placed in a forearm vein for blood sampling. After withdrawal of a baseline venous blood sample (4 ml), soluble paracetamol (1.5 g in 50 ml of water) was ingested. During the following 90 min, venous blood samples were obtained at 10, 20, 30, 40, 50, 60, 70 and 90 min. These samples were centrifuged and analysed for concentration of paracetamol using an enzymatic colorimetric assay (Cambridge Life Sciences, Cambridgeshire, UK).[10] The method is based on the use of an enzyme specific for the amide bond of acylated aromatic amines. It cleaves the paracetamol molecule, yielding p-aminophenol, which reacts specifically with o-cresol in ammoniacal copper solution to produce a blue colour. The paracetamol assay is specific for the parent compound and does not detect paracetamol metabolites.[11] At a concentration of 0.45 mmol litre^{-1} and a SD of 0.005 mmol litre^{-1},

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intra-assay coefficient of variation is 1.0%; inter-assay coefficient of variation is 1.1%.[10] Sensitivity, defined as 2 SD from zero, is 0.01 mmol litre^{-1}.[10] In terms of sensitivity, linearity, precision and accuracy, the enzymic assay is closely comparable with established methods of analysis (high pressure liquid chromatography and gas chromatography) over the range 0–2.5 mmol litre^{-1}.[11]

Patients remained semi-recumbent during measurement of gastric emptying.[12] Measures of gastric emptying used were area under the plasma paracetamol–time curve (AUC) (using the trapezoidal rule), maximum plasma paracetamol concentration ($C_p$max) and time to achieve $C_p$max (tC_pmax). After 4–10 weeks following the preoperative measurements, gastric emptying was again measured, and STAI scoring completed.

Paired *t* tests were used to compare preoperative and postoperative measures of anxiety and preoperative and postoperative variables of gastric emptying. The association between gastric emptying and anxiety was analysed using multiple regression. Pearson's correlation coefficient was used to measure the association between STAI_{s-t} and AUC.

In the absence of evidence defining the threshold value for clinically significant reductions in AUC, we considered a reduction in AUC of 50% to be clinically relevant. To detect this reduction, with a power of 0.95, β=0.2, α=0.05 and using a one-tailed *t* test, a minimum of 12 patients in each group was required.

Results

We approached 25 patients to participate in the study; four declined. Thus data were obtained from 21 patients (of whom one declined postoperative measurements, and the investigators were unable to obtain sufficient blood samples from another). Within-patient comparisons were based on 20 (10 males, 10 females) and 19 (10 males, nine females) sets of data for anxiety questionnaires and gastric emptying variables, respectively (mean age 40.8 (range 19–63) yr, mean body mass index 24.8 (SD 4.4) kg m^{-2}). Surgical procedures performed were varicose vein excision (*n*=4), diagnostic laparoscopy (*n*=3), transurethral resection of the prostate (*n*=1), inguinal hernia repair (*n*=3), incisional hernia repair (*n*=1), uterine curettage (*n*=2), total abdominal hysterectomy (*n*=2), vaginal hysterectomy (*n*=1), ovarian cystectomy (*n*=1), orchidectomy (*n*=1), scar revision (*n*=1) and haemorrhoidectomy (*n*=1).

Based on within-patient comparisons, measures of anxiety, STAI_s (*P*=0.0004) and STAI_{s-t} (*P*=0.02), were greater before operation than 4–10 weeks after operation (table 1). $\text{APAIS}_{\text{anx}}$, $\text{APAIS}_{\text{inf}}$ and $\text{APAIS}_{\text{tot}}$ scores obtained before operation were mean 8.6 (SD 4.0), 5.5 (2.7) and 14.1 (5.2), respectively. The $\text{APAIS}_{\text{anx}}$ score was ≥11 (the threshold for significant anxiety)[7] in eight (38%) of 21 patients. There was no significant correlation between STAI_s and STAI_t (r^2=0.002), $\text{APAIS}_{\text{anx}}$ (r^2=0.24) or $\text{APAIS}_{\text{inf}}$ (r^2=0.12), or between STAI_t and $\text{APAIS}_{\text{inf}}$.

The rate of gastric emptying, as quantified by AUC (*P*=0.23) and $C_p$max (*P*=0.42), was similar before and after operation. Time to maximum plasma paracetamol concentration (tC_pmax) was greater after operation (37.6 (18.4) min *vs* 48.2 (25.1) min) (*P*=0.02) (table 2).

Table 1 Spielberger state trait anxiety inventory scores (STAI_s, STAI_t, STAI_{s-t}) before and after operation (mean (SD))

	Preoperative (*n*=21)	Postoperative (*n*=20)	*P*
STAI_t	36.4 (8.1)	32.8 (9.0)	0.053
STAI_s	35.4 (10.9)	25 (4.1)	0.0004
STAI_{s-t}	−0.95 (9.3)	−7.0 (7.2)	0.019

Table 2 Measures gastric emptying before and after operation, area under the plasma paracetamol absorption–time curve (AUC), maximum plasma paracetamol concentration ($C_p$max) and time to $C_p$max ($t\,C_p$max) (mean (SD))

	Preoperative (*n*=21)	Postoperative (*n*=19)	*P*
AUC (mmol litre^{-1} min)	11.8 (2.87)	12.3 (3.7)	0.23
$C_p$max (mmol litre^{-1})	0.20 (0.06)	0.20 (0.07)	0.42
$t\,C_p$max (min)	37.6 (18.4)	48.2 (25.1)	0.02

Table 3 *P* values for multiple regression analysis between measures of gastric emptying (area under plasma paracetamol–time curve (AUC), maximum plasma paracetamol concentration ($C_p$max), time to $C_p$max ($t\,C_p$max)), and measures of anxiety (Spielberger state trait anxiety inventory scores (STAI_s, STAI_t, STAI_{s-t}) and the Amsterdam preoperative anxiety and information scale ($\text{APAIS}_{\text{anx}}$)

	AUC	$C_p$max	$t\,C_p$max
STAI_s	0.40	0.06	0.13
STAI_t	0.82	0.16	0.55
STAI_{s-t}	0.86	0.81	0.36
$\text{APAIS}_{\text{anx}}$	0.69	0.48	0.93

Multiple regression analysis performed on the combined (pre- and postoperative) data demonstrated no association between measures of anxiety (STAI_s, STAI_t and $\text{APAIS}_{\text{anx}}$) and corresponding paracetamol indices of rate of gastric emptying (AUC, $C_p$max, tC_pmax) (table 3). The STAI_{s-t} score, a measure of the magnitude of situational anxiety relative to anxiety predisposition, was not significantly associated with the rate of gastric emptying (fig. 1).

Discussion

The principal finding of this study was that gastric emptying was not delayed by anxiety, as quantified using STAI_s, STAI_t or STAI_{s-t}. Previous work on this subject has yielded conflicting results. Marsh, Spencer and Nimmo, using a paracetamol absorption technique, found no difference in the rate of gastric emptying in patients 2–3 h before, compared with 2–5 days after elective surgery.[13] They concluded that preoperative anxiety did not influence the rate of gastric emptying. However, this was limited by the investigators' assumption of the presence of anxiety in preoperative patients. Subsequently, Simpson and Stakes reported that gastric emptying was delayed in patients with a low anxiety trait who developed a high anxiety state before operation.[9] The difference between state and trait scores (STAI_{s-t}) was taken as a measure of preoperative anxiety relative to anxiety predisposition. However, these investigators did not

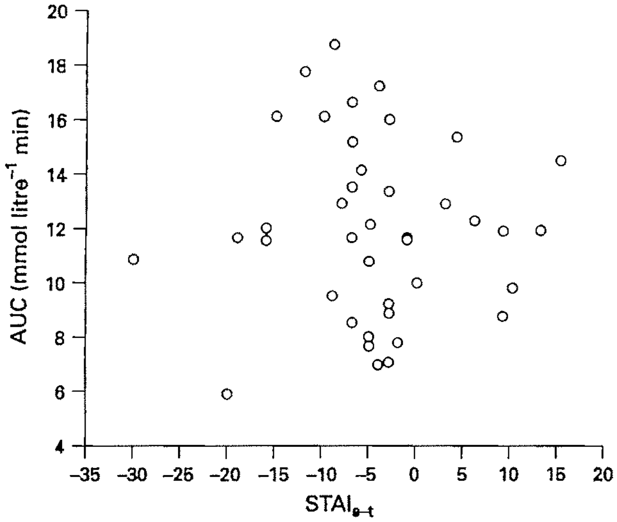

Figure 1 Relationship between area under the plasma paracetamol absorption–time curve (AUC), and the difference between the Spielberger state anxiety inventory scores and the Spielberger trait anxiety inventory scores (STAI$_{s-t}$).

report STAI$_s$ and STAI$_t$ scores from which this index was derived. Therefore, the presence of significant anxiety (the independent variable) had not been established in their study sample.

Between-patient comparison of a variable characterized by marked inter-patient variability[14] is potentially flawed. In our study, within-patient comparison of gastric emptying was made under two conditions, having established that one (preoperative state) was associated with a greater degree of anxiety (STAI$_s$, STAI$_t$ and STAI$_{s-t}$). We elected to exclude patients undergoing more major surgical procedures to increase the uniformity of the anxiogenic stimulus across the study sample. STAI$_s$ scores after operation (25 (4.1)) were lower than the normative level for US adults.[7] This may reflect patients' familiarity with the interviewers, study procedures and hospital surroundings during the second anxiety measurement.

Although tC_Pmax in the postoperative studies (48.2 (25.1) min) was significantly greater than that before operation (37.6 (18.4) min), this probably should not be interpreted to indicate that anxiety actually increases the rate of gastric emptying. The two other measures of gastric emptying (AUC, $C_P$max) were similar when pre- and postoperative values were compared. Regression analysis demonstrated no significant association between tC_Pmax and any measure of anxiety (table 3).

The paracetamol absorption technique used in this study is an accurate measure of the rate of gastric emptying of liquids, but not solids.[15] Because separate mechanisms govern these two processes, our conclusions refer only to liquids. However, it is likely that a preoperative delay in gastric emptying of liquids would result in a greater volume of gastric contents at induction of anaesthesia and therefore contribute to an increased risk of pulmonary aspiration of gastric contents.

Potential confounding factors which have been shown to influence gastric motility include phase of menstrual cycle,[16] circadian variation,[17] age[18] and posture.[12] Furthermore, one potential limitation is that the APAIS has, to date, been validated in Dutch, and not in English. In this study, no attempt was made to take account of the phase of menstrual cycle or circadian variation because the effect of both has been shown not to apply to gastric emptying of liquids.[16 17] Gastric emptying of liquids is slightly slower in the elderly (77 (range 70–84) yr) than in young adults (34 (range 21–63) yr). Among the younger adults, similar in age to those in our study (range 19–63 yr), there was no correlation between age and gastric emptying of liquids.[18] The effect of posture on gastric emptying did not influence our results because all patients were studied in the semi-recumbent position.

The amount of preoperative information a patient receives may influence recovery after surgery.[19] Patients may cope with the stress of surgery by "monitoring" (high information requirement) or "blunting" (low information requirement).[20] Failure to tailor information supply to suit an individual's needs may increase stress.[21] Previous studies have found a strong association between level of anxiety and need for information.[5] We did not find an association between anxiety scores and information requirement. This suggests that basing assessment of need for information on anxiety state or predisposition is unreliable.

A clinical implication of our findings is that the use of anxiolytic premedicants is unlikely to affect the volume of gastric contents at induction of anaesthesia, and thus the risk of pulmonary aspiration of gastric contents. These findings are consistent with those of previous studies.[22 23] Haavik and colleagues[22] evaluated the relationship between oral premedication, preoperative anxiety and gastric contents in patients undergoing elective surgery. Patients received one of two types of oral benzodiazepines or a placebo on the morning of surgery. As rated by patients, both benzodiazepines reduced anxiety, but gastric volume and pH did not correlate with the type of premedication or level of anxiety. Cote and colleagues[23] demonstrated that gastric pH and residual volume in preoperative children (3–17 yr) were independent of level of anxiety. Although anxiolysis may be desirable for other reasons, it is unlikely to decrease residual gastric volume.

In summary, the degree of anxiety experienced by adult patients before undergoing elective surgery was not associated with a delay in gastric emptying of liquids.

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References

1. Kallar SK, Everett LL. Potential risks and preventive measures for pulmonary aspiration: new concepts in preoperative fasting guidelines. *Anesthesia and Analgesia* 1993; 77: 171–182.
2. Stoelting RK. "NPO" and aspiration pneumonitis—changing perspectives. *American Society of Anesthesiologists 1995 Annual Refresher Course Lectures*, 1995; 432: 1–7.
3. Cote CJ. NPO after midnight for children—a reappraisal. *Anesthesiology* 1990; 72: 589–593.
4. Hardy J-F, Lepage Y, Bonneville-Chouinard N. Occurrence of gastroesophageal reflux on induction of anaesthesia does not correlate with the volume of gastric contents. *Canadian Journal of Anaesthesia* 1990; 37: 502–508.

5. Moerman N, van Dam FSAM, Muller MJ, Oosting H. The Amsterdam preoperative anxiety and information scale (APAIS). *Anesthesia and Analgesia* 1996; **82**: 445–451.
6. Nygren J, Thorell A, Hans Jacobsson H, Larsson S, Schnell P-O, Hylen L, Ljungqvist O. Preoperative gastric emptying—effects of anxiety and oral carbohydrate administration. *Annals of Surgery* 222; **6**: 728–734.
7. Speilberger CD, Gorsuch RL, Lushene RE. *State Trait Anxiety Inventory Manual.* Palo Alto, CA: Consulting Psychologists Press, 1970.
8. Heading RC, Nimmo J, Prescott LF, Tothill P. The dependence of paracetamol absorption on the rate of gastric emptying. *British Journal of Pharmacology* 1973; 47: 415–421.
9. Simpson KH, Stakes AF. Effect of anxiety on gastric emptying in preoperative patients. *British Journal of Anaesthesia* 1987; 59: 540–544.
10. Paracetamol assay kit. Cambridge Life Sciences plc, Cambridgeshire Business Park, Angel Drove, Ely, Cambridgeshire CB7 4DT, UK.
11. Brown SS, Campbell RS, Price CP, Rambohul E, Widdop B, Barbour H, Roberts JG, Burnett D, Atkinson T, Scawen MD, Hammond PM. Collaborative trial of an enzyme-based assay for the determination of paracetamol in plasma. *Annals of Clinical Biochemistry* 1983; **20**: 353–359.
12. Anvari M, Horowitz M, Fraser R, Maddox A, Myers J, Dent J, Jamieson GG. Effects of posture on gastric emptying of non-nutrient liquids and antropyloroduodenal motility. *American Journal of Physiology* 1995; **268**: 868–871.
13. Marsh RHK, Spencer R, Nimmo WS. Gastric emptying and drug absorption before and after surgery. *British Journal of Anaesthesia* 1983; 55: 242.
14. Petring OU, Flachs H. Inter- and intrasubject variability of gastric emptying in healthy volunteers measured by scintigraphy and paracetamol absorption. *British Journal of Clinical Pharmacology* 1990; **29**: 703–708.
15. Petring OU, Adelhoj B, Ibsen M, Poulsen HE. The relationship between gastric emptying of semisolids and paracetamol absorption. *British Journal of Clinical Pharmacology* 1986; 22: 659–662.
16. Gill RC, Murphy PD, Hooper HR, Bowes KL, Kingma YJ. Effect of the menstrual cycle on gastric emptying. *Digestion* 1987; **36**: 168–174.
17. Goo RH, Moore JG, Greenberg E, Alazraki NP. Circadian variations in gastric emptying of meals in humans *Gastroenterology* 1987; **93**: 515–518.
18. Horowitz M, Maddern GJ, Chatterton BE, Collins PJ, Harding PE, Shearman DJC. Changes in gastric emptying rates with age. *Clinical Sciences* 1984; **67**: 213–218
19. Devine EC. Effects of psychoeducational care for adult surgical patients: a meta-analysis of 191 studies. *Patient Education Council* 1992; **19**: 129–142.
20. Miller SM, Mangan CE. Interacting effects of information and coping style in adapting to gynecologic stress: should the doctor tell all? *Journal of Personal and Social Psychology* 1983; 45: 223–236.
21. Miller SM, Combs C, Stoddard E. Information, coping and control in patients undergoing surgery and stressful medical procedures. In: Steptoe A, Appels A, eds. *Stress, Personal Control and Health.* New York: Wiley, 1989; 107–130.
22. Haavik PE, Soreide E, Hofstad B, Steen PA. Does preoperative anxiety influence gastric fluid volume and acidity? *Anesthesia and Analgesia* 1992; 75: 91–94.
23. Cote CJ, Goudsouzian NJ, Liu LMP, Dedrick DF, Szyfelbein SK. Assessment of risk factors related to the acid aspiration syndrome in pediatric patients: gastric pH and residual volume. *Anesthesiology* 1982; **56**: 70–72.

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Prophylactic antiemetic therapy with granisetron in women undergoing thyroidectomy

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Summary

We have evaluated the efficacy and safety of granisetron, a selective 5-hydroxytryptamine type-3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) in women undergoing thyroidectomy. In a prospective, randomized, placebo-controlled, double-blind study, 100 ASA I patients, aged 30–57 yr, received placebo or granisetron at three different doses (20, 40 or 100 μg kg^{-1}) (n=25 each), i.v., immediately before induction of anaesthesia. A standard general anaesthetic technique was used. A complete response, defined as no PONV and no need for another rescue antiemetic during the first 3 h after anaesthesia, was seen in 36%, 44%, 92% and 92% of patients who received placebo, granisetron 20 μg kg^{-1}, 40 μg kg^{-1} and 100 μg kg^{-1}, respectively; corresponding values during the next 21 h after anaesthesia were 40%, 44%, 88% and 88% (P<0.05; overall Fisher's exact probability test). There were no clinically important adverse events in any group. We conclude that granisetron 40 μg kg^{-1} was an effective antiemetic for the prevention of PONV after thyroidectomy. Increasing the dose to 100 μg kg^{-1} provided no further benefit. (*Br. J. Anaesth.* 1998; **81**: 526–528).

Keywords: vomiting, nausea; vomiting, antiemetics; vomiting, nausea, surgical factors; pharmacology, granisetron; surgery, thyroidectomy

Postoperative nausea and vomiting (PONV) are common and unpleasant complications after surgery performed under general anaesthesia.[1] The reported incidence of PONV in patients undergoing thyroidectomy is 60–65% when no prophylactic antiemetic is given.[2 3] Most of the currently used antiemetics, antihistamines (e.g. hydroxyzine), butyrophenones (e.g. droperidol) and dopamine receptor antagonists (e.g. metoclopramide) have undesirable adverse effects, such as excessive sedation, hypotension, dry mouth, dysphoria, restlessness and extrapyramidal symptoms.[1] Granisetron, in common with ondansetron, is a selective antagonist of the 5-hydroxytryptamine type-3 (5-HT_3) receptor, and is also effective for the treatment of emesis in patients receiving cytotoxic drugs.[4]

Granisetron has a more potent and longer acting activity against cisplatin-induced emesis than ondansetron.[5] We have demonstrated recently that it reduces the incidence of PONV after gynaecological surgery.[6 7] We conducted a prospective, randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety of granisetron for the prevention of PONV in women undergoing general anaesthesia for thyroidectomy.

Patients and methods

After obtaining approval from the Institutional Review Board and informed consent, we studied 100 ASA I female patients, aged 30–57 yr, undergoing general anaesthesia for thyroidectomy. Patients who had gastrointestinal disease, those who had a history of motion sickness or previous PONV, or both, those who were menstruating, or those who had received antiemetic medication within 24 h before surgery were excluded.

Patients were allocated randomly to one of four groups (n=25 for each) to receive placebo or granisetron 20, 40 or 100 μg kg^{-1} i.v. before induction of anaesthesia according to a randomization list generated by a random number function in a computer spreadsheet. According to this list, identical syringes containing each drug were prepared by personnel not involved in the study.

Premedication comprised diazepam 5 mg orally, 60 min before induction of anaesthesia. Anaesthesia was induced with thiopental (thiopentone) 5 mg kg^{-1} i.v. and fentanyl 2 μg kg^{-1} i.v., and vecuronium 0.2 mg kg^{-1} i.v. was used to facilitate tracheal intubation. After tracheal intubation, anaesthesia was maintained with 1.0–3.0% (inspired concentration) isoflurane and 66% nitrous oxide in oxygen, with controlled ventilation adjusted to maintain an end-tidal concentration of carbon dioxide of 4.2–5.3 kPa. Neuromuscular block was achieved with vecuronium, as required. At cessation of surgery, atropine 0.02 mg kg^{-1} i.v. and neostigmine 0.04 mg kg^{-1} i.v. were administered for antagonism of neuromuscular block, and the trachea was extubated. Rectal temperature was monitored and maintained at 37±1°C using hot water warming pads. If two or more episodes of PONV occurred during the first

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Table 1 Patient characteristics, surgical and anaesthetic details, and postoperative analgesia, (mean (SD or range) or number). Patients who had experienced the menopause were excluded. No significant differences

	Placebo (n=25)	20 μg kg^{-1} (n=25)	40 μg kg^{-1} (n=25)	100 μg kg^{-1} (n=25)
Age(yr)	46.3(31–57)	47.2(30–57)	45.3(31–57)	46 0(30–57)
Height(cm)	156.7(6.4)	157.2(7.0)	157.5(7.4)	156.7(7.7)
Weight(kg)	52.3(5.0)	55.8(7.7)	52.6(6.5)	55.2(10.7)
Last menstrual cycle(days)[n]	15.3(3.2)[17]	16.2(2.9)[16]	16.1(3.6)[17]	15.4(3.8)[16]
Duration of operation(min)	142.9(47.4)	151.5(38.9)	146.6(38.0)	140.0(41.4)
Duration of anaesthesia(min)	178.1(54.3)	179.8(37.4)	175.8(40.7)	170.8(41.0)
Clinical status				
Euthyroidism(n)	20	21	20	20
Hyperthyroidism treated(n)	5	4	5	5
Postoperative analgesia				
Indomethacin(n)	15	15	16	15
Buprenorphine(n)	5	4	4	5

Table 2 Number (%) of patients with a complete response (no PONV, no rescue), nausea, retching or vomiting and those who required rescue antiemetic during the first 3 h (0–3 h) and the next 21 h (3–21 h) after anaesthesia. *P* values *vs* Placebo

	Placebo (n=25)	20 μg kg^{-1} P(n=25)	40 μg kg^{-1} P(n=25)		100 μg kg^{-1} P(n=25)		P
0–3 h after anaesthesia							
Complete response	9(36%)	11(44%)	0.387	23(92%)	0.001	23(92%)	0.001
Vomiting	8(32%)	6(24%)	0.377	1(4%)	0.012	1(4%)	0.012
Retching	2(8%)	1(4%)	0.5	0(0%)	0.245	0(0%)	0.245
Nausea	8(32%)	8(32%)	1.0	2(8%)	0.037	2(8%)	0.037
Rescue	7(28%)	5(20%)	0.371	0(0%)	0.048	0(0%)	0.048
3–24 h after anaesthesia							
Complete response	10(40%)	11(44%)	0.5	22(88%)	0.001	22(88%)	0.001
Vomiting	7(28%)	6(24%)	0.5	1(4%)	0.024	1(4%)	0.024
Retching	2(8%)	2(8%)	1.0	1(4%)	0.5	1(4%)	0.5
Nausea	8(32%)	7(28%)	0.5	2(8%)	0.037	2(8%)	0.037
Rescue	7(28%)	5(20%)	0.371	0(0%)	0.048	0(0%)	0 048

24 h after anaesthesia, another rescue antiemetic (e.g. metoclopramide) was given. Postoperative analgesia was provided with indomethacin 50 mg, as required, for moderate pain, and buprenorphine 0.2 mg i.m. for severe pain.

All episodes of PONV (nausea, retching and vomiting) were recorded during the first 24 h after anaesthesia (i.e. 0–3 h in the post-anaesthesia unit and 3–24 h in the ward) by direct questioning by specifically trained nurses without knowledge of which drugs the patients had received, or by spontaneous complaint by the patients. The nurses asked the patients if retching or vomiting had occurred and if they felt nauseated, with only two possible answers (yes/no). Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; retching was defined as the laboured, spasmodic, rhythmic contractions of the respiratory muscles; vomiting was defined as the forceful expulsion of gastric contents from the mouth.[1] Complete response (i.e. emesis-free) was defined as no PONV and no need for rescue antiemetic medication. Details of other adverse events throughout the study were recorded by follow-up nurses who interviewed the patients and recorded spontaneous complaints.

Statistical analyses of the data between the treatment groups were performed by ANOVA with Bonferroni correction for multiple comparison, chi-square test or Fisher's exact probability test, as appropriate. $P<0.05$ was considered significant. All values are expressed as mean (SD, range) or number (%). Twenty-five patients per group were sufficient to detect a difference with a=0.05 and power (1–ß)=0.8.

Results

Patient characteristics and details of anaesthesia are summarized in table 1. There were no significant differences between groups.

A complete response 0–3 h after anaesthesia was seen in 36% of patients who received placebo, 44% with granisetron 20 μg kg^{-1}, 92% with granisetron 40 μg kg^{-1} and 92% with granisetron 100 μg kg^{-1}; corresponding values for 3–24 h after anaesthesia were 40%, 44%, 88% and 88%. Thus significantly more patients had a complete response within the first 24 h after anaesthesia in the granisetron 40 μg kg^{-1} and 100 μg kg^{-1} groups compared with placebo ($P<0.05$). There was no difference between placebo and granisetron 20 μg kg^{-1} (table 2).

Seven of 25 patients who had received placebo and five of those who had received granisetron 20 μg kg^{-1} required rescue antiemetic for severe PONV during the first 3 h and the next 21 h after anaesthesia (i.e. two or more episodes of PONV), compared with none who received granisetron 40 μg kg^{-1} or 100 μg kg^{-1} ($P<0.05$) (table 2).

The most common adverse events were headache and dizziness, which were relatively mild. There were no differences in the incidence of adverse effects (table 3).

Table 3 Adverse events. Values are number (%). There were no significant differences

	Placebo (n=25)	20 μg kg^{-1} (n=25)	40 μg kg^{-1} (n=25)	100 μg kg^{-1} (n=25)
0-3 h after anaesthesia				
Any adverse effects	5(20%)	4(16%)	4(16%)	5(20%)
Headache	2(8%)	2(8%)	2(8%)	2(8%)
Dizziness	2(8%)	1(4%)	1(4%)	2(8%)
Others(constipation, muscle pain)	1(4%)	1(4%)	1(4%)	1(4%)
3-24 h after anaesthesia				
Any adverse efects	4(16%)	4(16%)	4(16%)	4(16%)
Headache	2(8%)	2(8%)	2(8%)	2(8%)
Dizziness	1(4%)	1(4%)	1(4%)	1(4%)
Others (constipation, muscle pain)	1(4%)	1(4%)	1(4%)	1(4%)

Discussion

Postoperative nausea and vomiting (PONV) are distressing side effects of anaesthesia and surgery, with a high incidence after thyroidectomy.[2,3] The aetiology of PONV remains unclear, but is probably related to several factors, including age and sex of the patient (mostly middle-aged women), and intense peroperative vagal stimulation (surgical handling of neck structures).[3] Several factors, including obesity, anaesthetic technique and postoperative pain, are considered to increase the incidence of PONV.[1] However, in our study the groups were similar in patient characteristics, surgical procedure, anaesthetic administered and analgesics used after operation. Therefore, the difference in complete response can be attributed to the study drug.

We found a high incidence of PONV during the first 24 h after anaesthesia (64% for 0–3 h after anaesthesia and 60% for 3–24 h after anaesthesia) in patients who had received placebo. This is comparable with an incidence of nearly 60% reported previously.[2,3]

Granisetron has already been reported to be effective for the treatment of vomiting in patients receiving cytotoxic drugs.[4] It has also been reported that granisetron is effective in the prevention of PONV after gynaecological surgery.[6,7] We have demonstrated that there was a complete response (no PONV, no rescue) in significantly more patients who received granisetron 40 μg kg^{-1} or 100 μg kg^{-1} compared with those who had received placebo. The exact mechanism of granisetron in preventing PONV is not known, but it has been suggested that it may act on sites containing 5-HT$_3$ receptors with demonstrated antiemetic effects.[8]

The effective dose of granisetron is between 40 and 80 μg kg^{-1} for the treatment of cancer therapy-induced emesis.[9] We could find no report to determine the minimum effective dose for the prevention of PONV in patients undergoing thyroidectomy. We have demonstrated that the efficacy of granisetron 40 μg kg^{-1} was similar to that of 100 μg kg^{-1} for the prevention of PONV, and that there was no difference between placebo and granisetron 20 μg kg^{-1}. In addition, the severity of PONV was also reduced with granisetron 40 or 100 μg kg^{-1}, as no patient required rescue medication for the treatment of two or more episodes of PONV, compared with several patients who received placebo or granisetron 20 μg kg^{-1}. These data suggest that granisetron in a minimum dose of 40 μg kg^{-1} was effective for the prevention of PONV after thyroidectomy.

The most frequent adverse events were headache and dizziness but there were no differences in the incidence of these symptoms between groups.

In summary, granisetron 40 μg kg^{-1} was an effective antiemetic for the prevention of PONV in female patients undergoing thyroidectomy. Increasing the dose to 100 μg kg^{-1} provided no further benefit.

References

1. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology* 1992; 77: 162–184.
2. Dejonckheere M, DeloofT, Dustin N, Ewalenko P. Alizapride in the prevention of post-thyroidectomy emetic sequelae. *European Journal of Anaesthesiology* 1990; 7: 421–427.
3. Ewalenko P, Janny M, Dejonckheere M, Andry G, Wyns C. Antiemetic effect of subhypnotic doses of propofol after thyroidectomy. *British Journal of Anaesthesia* 1996; 77: 463–467
4. Bermudez J, Boyle EA, Minter WD, Sanger GJ. The antiemetic potential of the 5-hydroxytryptamine, receptor antagonist BRL 43694. *British Journal of Cancer* 1988; 58: 644–650.
5. Andrews PLR, Bhandari P, Davey PT, Bingham S, Marr HE, Blower PR. Are all 5-HT$_3$ receptor antagonists the same? *European Journal of Cancer* 1992; 28. S2–6.
6. Fujii Y, Tanaka H, Toyooka H. Reduction of postoperative nausea and vomiting with granisetron. *Canadian Journal of Anaesthesia* 1994; 41: 291–294.
7. Fujii Y, Tanaka H, Toyooka H. Optimal anti-emetic dose of granisetron for preventing postoperative nausea and vomiting. *Canadian Journal of Anaesthesia* 1994; 41: 794–797.
8. Carmichael J, Cantwell BMJ, Edwards CM, Zussmann BD, Thompson S, Rapeport WG, Hariis AL. A pharmacokinetic study of granisetron (BRL 43694A), a selective 5-HT$_3$ receptor antagonist: correlation of anti-emetic response. *Cancer Chemotherapy and Pharmacology* 1989; 24: 45–49.
9. Furue H, Oota K, Taguchi T, Niitani H. Clinical evaluation of granisetron against nausea and vomiting induced by anti-cancer drugs. Optimal dose-finding study (Japanese). *Journal of Clinical Therapy and Medicine* 1990; 6 (Suppl.): 49–61.

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Laser stimulation of acupuncture point P6 reduces postoperative vomiting in children undergoing strabismus surgery

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Summary

We conducted a double-blind, randomized, placebo-controlled study to investigate the effectiveness of P6 acupuncture on postoperative vomiting in children undergoing strabismus surgery. Acupuncture was performed by laser stimulation with a low-level laser. Laser stimulation of P6 was administered 15 min before induction of anaesthesia and 15 min after arriving in the recovery room. In the laser stimulation group, the incidence of vomiting was significantly lower (25%) than that in the placebo group (85%). (*Br. J. Anaesth.* 1998; **81**: 529–532).

Keywords: anaesthesia, paediatric; acupuncture; vomiting, incidence; vomiting, nausea, surgical factors; surgery, ophthalmological

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Postoperative vomiting is one of the most frequent complications after strabismus surgery in children. The incidence of postoperative vomiting has been reported as 40–88%.[1–6] Several pharmacological studies have been performed to reduce this high incidence.[1 2 5 7–11]

A non-pharmacological method for the prevention of postoperative vomiting is stimulation of an acupuncture point called Pericard 6 (P6, Neiguan). Numerous studies have shown that stimulation of P6 with acupuncture reduces postoperative vomiting.[12–16] However, needle acupuncture and acupressure of P6 appear ineffective in the reduction of postoperative vomiting in children.[17–20]

In this study, we used laser acupuncture to stimulate P6.[21–23] A laser beam generated by a low-level laser diode stimulates the acupuncture point. This form of acupuncture is painless and especially suitable in awake children. Our aim was to evaluate the antiemetic effect of laser stimulation of P6 in children undergoing strabismus surgery compared with placebo.

Patients and methods

The study was approved by the Ethics Committee of the University of Innsbruck, Austria and written, informed consent was obtained from the parents of the children. We studied 40 children, ASA I or II, aged 3–12 yr, undergoing strabismus surgery. We excluded those with gastric or intestinal diseases, emesis and vomiting in the previous week, and those who received any medical therapy immediately before surgery.

In this double-blind, prospective study, each child was allocated randomly to one of two groups. Acupuncture was performed on acupuncture point Pericard 6 (P6). P6 is located at the wrist between the tendons of the palmaris longus and flexor carpi radialis, 2 Cun proximal from the distal palmar crease. One Cun is equivalent to the width of the patient's thumb across the interphalangeal joint. Patients in group A underwent laser stimulation of P6. We used a low-level laser with the following characteristics: diode laser with continuous laser beam; power output 10 mW; wavelength 670 nm laser (Minilaser 2010F, Helbo-Medizintechnik, Gallspach, Austria). Laser stimulation was performed on each P6 bilaterally over 30 s, 15 min before induction of anaesthesia and 15 min after arriving in the recovery room. In group B, the same low-level laser was held on P6, but the laser beam was not activated. Neither the children nor their parents were able to tell if the laser was active. Both laser and placebo acupuncture were performed by the same investigator.

All patients were allowed solid food or clear fluids up to 6 h before anaesthesia. Oral premedication with midazolam 0.4 mg kg^{-1} and atropine 0.02 mg kg^{-1} was given 1 h before transfer to the operating room. For painless placement of an i.v. cannula, each child received 5% EMLA cream (Astra, Austria) on a vein in the left cubita or on the back of the left hand.

Strabismus repair was performed under general anaesthesia. Thiopental 5 mg kg^{-1}, rocuronium 0.6 mg kg^{-1} and fentanyl 2 μg kg^{-1} were administered i.v. for induction of anaesthesia. After intubation, anaesthesia was maintained with 2–3% sevoflurane and 66.6% nitrous oxide in oxygen with controlled ventilation. Fluid deficit was replaced by an i.v. mixture of three parts Ringer's lactate solution and two parts 5% dextrose. Residual neuromuscular block was antagonized with prostigmine 0.05 mg kg^{-1} and atropine 0.025 mg kg^{-1}. Immediately after arrival in the recovery room, all patients received paracetamol suppositories 10 mg kg^{-1} for postoperative analgesia. The second laser stimulation was performed 15 min after arrival in the recovery room. After the children were awake and had stable vital functions, they were transferred to their rooms. Dimenhydrinate suppositories 50 mg were given as rescue antiemetic.

The incidence of vomiting was recorded by the nursing staff in the recovery room and on the ward over 24 h.

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Table 1 Patient characteristics (mean (SD) or number) in the two groups

	Laser acupuncture (*n* = 20)	Placebo acupuncture (*n* = 20)
Age (yr)	5.9 (1.8)	6.3 (1.9)
Sex (M/F)	9/11	10/10
Weight (kg)	21.5 (8.46)	24.1 (7.5)
Anaesthesia duration (min)	72.6 (18.2)	66.42 (18.0)
Surgery duration (min)	54. 15 (17.3)	46 7 (12.9)
No. of muscles repaired, right side	1.82 (0.52)	1.92 (0.73)
No. of muscles repaired, left side	1.78 (0.58)	1.53 (0.51)

Table 2 Incidence of postoperative vomiting (number (%)) in the two groups. P=0.0001 between groups

Group	Vomiting	Non-Vomiting
Laser acupuncture (*n*=20)	5 (25%)	15 (75%)
Placebo acupuncture (*n*=20)	17 (85%)	3 (15%)

Table 3 Appearance of first episode of vomiting after surgery (number (%)) in the two groups

Group	0–2 h	0–6 h	0–12 h	12–24h
Laser acupuncture (*n*=20)	0 (0%)	3 (15%)	4 (20%)	1 (5%)
Placebo acupuncture (*n*=20)	6 (30%)	13 (65%)	14 (70%)	3 (15%)

The number of patients required was determined by power analysis. We assumed that the incidence of vomiting would be 70% in the control group and 30% in the acupuncture group. P<0.05 was regarded as statistically significant. Statistical analysis was performed using SPSS 6.1 (SPSS Inc.). Fisher's exact test was used to determine the incidence of vomiting, and the unpaired *t* test to analyse patient data.

Results

There were no significant differences between the groups in age, sex distribution, ASA status, weight, height, duration of anaesthesia, duration of surgery or number of repaired muscles (table 1). Because of difficult placement of the i.v. cannula in two awake children, general anaesthesia was induced with sevoflurane administered by mask (one child in each group).

Compared with the placebo group, the incidence of vomiting was significantly lower in the acupuncture group (P=0.0001). In the first 24 h after surgery, vomiting occurred in five (25%; 95% confidence interval (CI) 8.56–49.10%) of 20 patients in the laser acupuncture group and in 17 (85%; 95% CI 62.11–96.79%) of 20 children in the placebo group (table 2).

In the laser acupuncture group, no patient vomited in the first 2 h after surgery. In the same interval, vomiting occurred in six children in the placebo group. Within the first 6 h, three (15%) children in the laser acupuncture group and 13 (65%) in the placebo group vomited. During 0–12 h after surgery, the incidence of vomiting in children who had received laser acupuncture (20%) differed from those who had placebo acupuncture (70%). In the acupuncture group one child, and in the placebo group three children, vomited for the first time 12–24 h after surgery (table 3).

Two children who received laser acupuncture and 14 children in the placebo group required antiemetic rescue therapy.

Discussion

Using laser stimulation of acupuncture point P6, we have demonstrated a significant reduction in postoperative vomiting in children undergoing strabismus surgery. These results do not correspond with previous studies in paediatric patients, in whom needle acupuncture, acupressure or transcutaneous electrical stimulation of P6 was performed to reduce postoperative vomiting.[17–20]

Acupuncture of P6 in adult patients has been shown to reduce the incidence of postoperative vomiting.[13 24–26] Most of these studies were conducted in gynaecological patients and in all, acupuncture was carried out before induction of anaesthesia. Timing of acupuncture seems to be important for the effectiveness of P6[27 28]; it seems important that stimulation is performed before induction of anaesthesia. Dundee and Milligan[28] showed no antiemetic effect of P6 when opioids were administered before acupuncture. Weightman, Zacharias and Herbison were unable to demonstrate an antiemetic effect when acupuncture was performed during general anaesthesia[29].

Yentis and Bissonnette[18] performed acupuncture over 5 min on P6 in anaesthetized children immediately before starting surgery. In this study, the investigators found no difference in the incidence of postoperative vomiting after droperidol (41%), acupuncture (43%) and acupuncture–droperidol (34%). Because there was no placebo group, Yentis and Bissonnette[18] have shown only that acupuncture and the combination of acupuncture and droperidol did not decrease the incidence of postoperative vomiting compared with droperidol alone. This seems important because other investigations using droperidol showed a reduction in postoperative vomiting in children undergoing strabismus surgery.[1 10 30]

Schwager, Baines and Meyer used transcutaneous electrical stimulation of P6 to prevent postoperative vomiting in children undergoing circumcision and orchidopexy surgery.[19] This method is non-invasive, but they stimulated P6 in anaesthetized patients. The reason why electrical stimulation did not prevent postoperative vomiting could be the same as in all other studies in which acupuncture of P6 was performed after induction of anaesthesia. Additionally, transcutaneous electrical stimulation is shorter acting and less effective than needle acupuncture.[26,31]

Compared with needle acupuncture, acupressure allows painless stimulation of P6 [24,25,32,33] and is therefore useful in children. However, this method has failed in paediatric patients undergoing strabismus surgery.[20] It may be that stimulation of P6 with acupressure alone was insignificant to prevent postoperative vomiting in children after strabismus surgery.[34] Previous studies with acupressure in adult patients have also shown that acupressure reduced nausea but not vomiting.[32]

If the prevention of postoperative vomiting by stimulation of P6 requires awake patients in order to be effective, needle acupuncture is unsuitable in paediatric patients. In contrast with invasive needling, laser stimulation of acupuncture points allows painless acupuncture. Our results showed that painless laser acupuncture reduced postoperative vomiting in paediatric patients undergoing strabismus surgery, primarily in the early postoperative period.

In contrast with previous studies, we performed laser stimulation of P6 before induction of anaesthesia and in the recovery room. Each acupuncture point was stimulated for 30 s. The first stimulation of P6 was conducted 15 min before induction of anaesthesia and the second 15 min after surgery. This may account for the good antiemetic effect. Most of the recent studies showed an antiemetic effect of P6 when acupuncture was performed only once, immediately before induction of anaesthesia.[12,13,26] Ho and colleagues demonstrated a significant reduction in postoperative vomiting in adult patients when postoperative electroacupuncture was performed.[35] Yang and co-workers also found an antiemetic effect when a 50% glucose solution was injected after operation into P6.[36] Whether single laser stimulation of P6 is also sufficient to reduce postoperative vomiting after strabismus surgery in paediatric patients should be examined in further studies.

The antiemetic effects of P6 stimulation by a low-level laser were similar to those reported in studies which investigated the effects of antiemetic agents in children undergoing strabismus surgery.[1,2,7,10,30,37–42] Therapy with drugs such as ondansetron, droperidol and metoclopramide, however, is often associated with side effects.[43–46] In comparison, stimulation of P6 with a low-level laser has no known side effects. However, it must be remembered that direct laser irradiation of the retina should be avoided by laser-protection glasses and correct handling.

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References

1. Abramowitz MD, Oh TH, Epstein BS, Ruttimann UE, Friendly DS. The antiemetic effect of droperidol following outpatient strabismus surgery in children. *Anesthesiology* 1983; 59: 579–583.
2. Rose JB, Martin TM, Corddry DH, Zagnoev M, Kettrick RG. Ondansetron reduces the incidence and severity of poststrabismus repair vomiting in children. *Anesthesia and Analgesia* 1994; 79: 486–489.
3. Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; 69 (Suppl. 1): 24S–32S.
4. Standl T, Wilhelm S, von Knobelsdorff G, Schulte am Esch J. Propofol reduces emesis after sufentanil supplemented anaesthesia in paediatric squint surgery. *Acta Anaesthesiologica Scandinavica* 1996; 40: 729–733.
5. Karlsson E, Larsson LE, Nilsson K. The effects of prophylactic dixyrazine on postoperative vomiting after two different anaesthetic methods for squint surgery in children. *Acta Anaesthesiologica Scandinavica* 1993; 37: 45–48.
6. Tramer M, Moore A, McQuay H. Prevention of vomiting after paediatric strabismus surgery: a systematic review using the numbers-needed-to-treat method. *British Journal of Anaesthesia* 1995; 75: 556–561.
7. Broadman LM, Ceruzzi W, Patane PS, Hannallah RS, Ruttimann U, Friendly D. Metoclopramide reduces the incidence of vomiting following strabismus surgery in children. *Anesthesiology* 1990; 72: 245–248.
8. Chisakuta AM, Mirakhur RK. Anticholinergic prophylaxis does not prevent emesis following strabismus surgery in children. *Paediatric Anaesthesia* 1995; 5: 97–100.
9. Larsson S, Jonmarker C. Postoperative emesis after paediatric strabismus surgery: the effect of dixyrazine compared to droperidol. *Acta Anaesthesiologica Scandinavica* 1990; 34: 227–230.
10. Lerman J, Eustis S, Smith DR. Effect of droperidol pretreatment on postanesthetic vomiting in children undergoing strabismus surgery. *Anesthesiology* 1986; 65: 322–325.
11. Watcha MF, Simeon RM, White PF, Stevens JL. Effect of propofol on the incidence of postoperative vomiting after strabismus surgery in pediatric outpatients. *Anesthesiology* 1991; 75: 204–209.
12. Dundee JW, Chestnutt WN, Ghaly RG, Lynas AG. Traditional Chinese acupuncture: a potentially useful antiemetic? *British Medical Journal* 1986; 293: 583–584.
13. Al-Sadi M, Newman B, Julious SA. Acupuncture in the prevention of postoperative nausea and vomiting. *Anaesthesia* 1997; 52: 658–661.
14. Stein DJ, Birnbach DJ, Danzer BI, Kuroda MM, Grunebaum A, Thys DM. Acupressure versus intravenous metoclopramide to prevent nausea and vomiting during spinal anesthesia for cesarean section. *Anesthesia and Analgesia* 1997, 84: 342–345.
15. Ghaly RG, Fitzpatrick KT, Dundee JW. Antiemetic studies with traditional Chinese acupuncture. A comparison of manual needling with electrical stimulation and commonly used antiemetics. *Anaesthesia* 1987; 42: 1108–1110
16. Dundee JW, McMillan CM. Clinical uses of P6 acupuncture antiemesis. *Acupuncture and Electro-Therapeutics Research* 1990; 15: 211–215.
17. Yentis SM, Bissonnette B. P6 acupuncture and postoperative vomiting after tonsillectomy in children. *British Journal of Anaesthesia* 1991; 67: 779–780.
18. Yentis SM, Bissonnette B. Ineffectiveness of acupuncture and droperidol in preventing vomiting following strabismus repair in children. *Canadian Journal of Anaesthesia* 1992; 39: 151–154.
19. Schwager KL, Baines DB, Meyer RJ. Acupuncture and postoperative vomiting in day-stay paediatric patients. *Anaesthesia and Intensive Care* 1996; 24: 674–677.
20. Lewis IH, Pryn SJ, Reynolds PI, Pandit UA, Wilton NC. Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction. *British Journal of Anaesthesia* 1991; 67: 73–78.
21. Kleinkort JA. Laser acupuncture: its use in physical therapy. *American Journal of Acupuncture* 1984; 12: 51–56.
22. Bischko JJ. Use of the laser in acupuncture. *Acupuncture and Electro-Therapeutics Research* 1980; 5: 29–40.
23. Brockhaus A, Elger CE. Hypalgesic efficacy of acupuncture on experimental pain in man. Comparison of laser acupuncture and needle acupuncture. *Pain* 1990; 43: 181–185.
24. Allen DL, Kitching AJ, Nagle C P6 acupressure and nausea and vomiting after gynaecological surgery. *Anaesthesia and Intensive Care* 1994; 22: 691–693.
25. Fan CF, Tanhui E, Joshi S, Trivedi S, Hong Y, Shevde K. Acupressure treatment for prevention of postoperative nausea and vomiting. *Anesthesia and Analgesia* 1997; 84: 821–825.
26. Dundee JW, Ghaly RG, Bill KM, Chestnutt WN, Fitzpatrick KT, Lynas AG. Effect of stimulation of the P6 antiemetic

point on postoperative nausea and vomiting. *British Journal of Anaesthesia* 1989; **63**: 612–618.

27. Dundee JW, Ghaly RG. Does the timing of P6 acupuncture influence its efficacy as a postoperative antiemetic? *British Journal of Anaesthesia* 1989; **63**: 630P.
28. Dundee JW, Milligan KR. Influence of intraoperative acupuncture and droperidol on postoperative emesis. *British Journal of Anaesthesia* 1988; **61**: 116P–117P.
29. Weightman WM, Zacharias M, Herbison P. Traditional Chinese acupuncture as an antiemetic. *British Medical Journal* 1987; **295**: 1379–1380.
30. Christensen S, Farrow-Gillespie A, Lerman J. Incidence of emesis and postanesthetic recovery after strabismus surgery in children: a comparison of droperidol and lidocaine. *Anesthesiology* 1989; **70**: 251–254.
31. Dundee JW, Yang J, McMillan C. Non-invasive stimulation of the P6 (Neiguan) antiemetic acupuncture point in cancer chemotherapy. *Journal of the Royal Society of Medicine* 1991; **84**: 210–212.
32. Barsoum G, Perry EP, Fraser IA. Postoperative nausea is relieved by acupressure. *Journal of the Royal Society of Medicine* 1990; **83**: 86–89.
33. Gieron C, Wieland B, von der Laage D, Tolksdorf W. Acupressure in the prevention of postoperative nausea and vomiting. *Anaesthesist* 1993; **42**: 221–226.
34. Dundee JW, McMillan CM. P6 acupressure and postoperative vomiting. *British Journal of Anaesthesia* 1992; **68**: 225–226.
35. Ho RT, Jawan B, Fung ST, Cheung HK, Lee JH. Electro-acupuncture and postoperative emesis. *Anaesthesia* 1990; **45**: 327–329.
36. Yang LC, Jawan B, Chen CN, Ho RT, Chang KA, Lee JH. Comparison of P6 acupoint injection with 50% glucose in water and intravenous droperidol for prevention of vomiting after gynaecological laparoscopy. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 192–194.
37. Abramowitz MD, Elder PT, Friendly DS, Broughton WL, Epstein BS. Antiemetic effectiveness of intraoperatively administered droperidol in pediatric strabismus outpatient surgery—preliminary report of a controlled study. *Journal of Pediatric Ophthalmology and Strabismus* 1981; **18**: 22–27.
38. Fujii Y, Tanaka H, Toyooka H. Granisetron reduces vomiting after strabismus surgery and tonsillectomy in children. *Canadian Journal of Anaesthesia* 1996; **43**: 35–38.
39. Klockgether-Radke A, Neumann S, Neumann P, Braun U, Muhlendyck H. Ondansetron, droperidol and their combination for the prevention of post-operative vomiting in children. *European Journal of Anaesthesiology* 1997; **14**: 362–367.
40. Lin DM, Furst SR, Rodarte A. A double-blinded comparison of metoclopramide and droperidol for prevention of emesis following strabismus surgery. *Anesthesiology* 1992; **76**: 357–361.
41. Litman RS, Wu CL, Lee A, Griswold JD, Voisine R, Marshall C. Prevention of emesis after strabismus repair in children: a prospective, double-blinded, randomized comparison of droperidol versus ondansetron. *Journal of Clinical Anesthesia* 1995; **7**: 58–62.
42. Shende D, Mandal NG. Efficacy of ondansetron and metoclopramide for preventing postoperative emesis following strabismus surgery in children. *Anaesthesia* 1997; **52**: 496–500.
43. Melnick B, Sawyr R, Karambelkar D, Phitayakorn P, Lim Uy NT, Patel R. Delayed side effects of droperidol after ambulatory general anesthesia. *Anesthesia and Analgesia* 1989; **69**: 748–751.
44. Melnick BM. Extrapyramidal reactions to low-dose droperidol. *Anesthesiology* 1988; **69**: 424–426.
45. Smith RN. Safety of ondansetron. *European Journal of Cancer and Clinical Oncology* 1989; **25** (Suppl. 1): S47–S50.
46. Caldwell G, Rains G, McKiterick K. An unusual reaction to preoperative metoclopramide. *Anesthesiology* 1987; **67**: 854–855.

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Perioperative reliability of an on-site prothrombin time assay under different haemostatic conditions

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Summary

Perioperative use of laboratory coagulation assays is limited by the delay in obtaining results. The management of haemostasis during major surgical procedures requires rapid and accurate measurement of the prevailing coagulation status. In this prospective study, we have evaluated the reliability of on-site prothrombin time assessed by the portable coagulation monitor CoaguChek-Plus compared with standard laboratory assays during elective non-cardiac surgery. Sixty-two patients were assigned to one of three groups: group A=normal preoperative coagulation where minor intraoperative blood loss is expected; group B=normal preoperative coagulation where major intraoperative blood loss is expected; and group C=preoperative anticoagulation and minor intraoperative blood loss expected. On-site prothrombin time and laboratory prothrombin time showed poor correlation in group A (r^2=0.24; bias (2 SD) 1.80 (3.34) s) and group B (r^2=0.30; 1.43 (3.12) s). The correlation in group C was better (r^2=0.71; 1.41 (1.92) s). We conclude that prothrombin time measured with the CoaguChek-Plus monitor did not appear to be suitable for the management of haemostasis. (*Br. J. Anaesth.* 1998; **81**: 533–536).

Keywords: blood, coagulation; blood, haemostasis; measurement techniques, coagulation

Intraoperative assessment of coagulation is of major concern, as it may alter rapidly during surgery as a result of both major blood loss and volume replacement with colloids, crystalloids and blood components.[1] Furthermore, an increasing number of patients with compromised haemostatic potential present for surgery. The prothrombin time (PT) assay is used in the perioperative period as a routine measure of the extrinsic pathway of coagulation. The clinical use of most laboratory coagulation assays, including PT, continues to be restricted by the delay in obtaining results. Rapid determination of PT may be helpful in the case of major bleeding and coagulopathy. Despotis and colleagues demonstrated that the use of on-site coagulation assays can reduce the use of blood products, decrease operating time and minimize chest tube drainage in cardiac surgery.[2]

The portable coagulation monitor CoaguChek-Plus (Boehringer Mannheim, Germany, formerly Biotrack 512, Ciba-Corning, Medfield, MA, USA) has been shown to measure accurately intraoperative on-site PT in less than 3 min.[3 4] Comparison of results with those of standard laboratory assays has been made in cardiac[2–5] and gynaecological surgery.[6] The purpose of our prospective study was to evaluate the reliability of CoaguChek-Plus prothrombin time (CC-PT) in comparison with simultaneous standard laboratory prothrombin time (LAB-PT) assays under different haemostatic conditions during elective non-cardiac surgery.

Patients and methods

After obtaining approval from the Ethics Committee and informed patient consent, we studied 62 patients with no history of bleeding. Patients were allocated to one of three groups: group A=normal preoperative coagulation and minor intraoperative blood loss expected; group B=normal preoperative coagulation and major intraoperative blood loss expected; and group C=preoperative oral anticoagulation with phenprocoumon (Marcoumar) or acenocoumarol (Sintrom), discontinued before surgery, or high-dose i.v. heparin. The inclusion criterion for those receiving oral anticoagulants was a laboratory PT <65% (corresponding to an international normalized ratio (INR) of >1.4) on the day before surgery. The inclusion criterion for patients receiving heparin was a daily dose of heparin >15 000 u. (Liquemin). Assessment of PT was performed on 3–5 separate occasions: (1) before operation, after induction of anaesthesia; (2) during operation, up to three times, depending on the length of the surgical procedure and amount of blood loss and fluid replacement; and (3) after operation, before patient transport from the operating theatre to the recovery room or intensive care unit.

CC-PT measurements were performed strictly in accordance with the manufacturer's instructions. The technical and methodological aspects of the CoaguChek-Plus monitor have been described by Lucas and colleagues.[7] All blood samples were obtained from a non-heparinized central venous catheter, the catheter being rinsed with 20 ml of saline beforehand. 10 ml of blood were withdrawn and discarded before sampling. For the CoaguChek-Plus, one drop of the sampled blood was applied immediately to the inserted CC-PT cartridge. For the

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Table 1 Perioperative packed cell volume (PCV) and intraoperative blood transfusion (mean (SD)). CC-PT=CoaguChek-Plus prothrombin time (PT) measurements; LAB-PT=laboratory PT measurements. $^{**}P<0.01$, $^{***}P<0.001$, significant differences in group B compared with both groups A and C

	Group A	Group B	Group C
Number of comparisons (CC-PT *vs* LAB-PT)	138	37	16
Preoperative PCV (%)	37.1 (7.1)	34.7 (10.6)	39.2 (3.9)
Postoperative PCV (%)	30.9 (6.7)	23.4 (3.7)**	31.2 (3.8)
Packed red blood cells transfused (ml)	820 (496)	2160 (684)***	350

standard laboratory assay, 10 ml of whole blood were drawn up into a citrate-containing glass tube and sent immediately to the laboratory. LAB-PT measurements were performed using the Electra 1600 C (Medical Laboratory Automation, Pleasantville, NY, USA) and thromboplastin Innovin (DADE Behring, Illinois, USA). The INR, calculated by the CoaguChek-Plus monitor, was compared with the INR of the laboratory assay.

STATISTICAL ANALYSIS

Comparisons between groups (packed cell volume (PCV), units of transfused blood) were made using analysis of variance (ANOVA) and the Bonferroni–Dunn test. Possible trends in the differences in consecutive measurements were analysed by ANOVA for repeated measures with the Greenhouse–Geisser correction. The correlation between CC-PT and LAB-PT measurements was determined by linear regression and bias analysis. $P<0.05$ was considered statistically significant. The statistical program used was StatView for Windows v. 4.57 (Abacus Concepts Inc.) running on an IBM personal computer.

Results

PCV values before and after operation and packed red blood cell requirements are shown in table 1. Preoperative PCV was similar in all groups. Group B had a significantly higher intraoperative need for packed red blood cells. After operation, following blood product use, PCV in group B was significantly lower than that in the two other groups.

Immediate preoperative PT measurements were similar in all groups. There was an over-reading (bias) of 1.41 s (group C) to 1.80 s (group A) in CC-PT compared with LAB-PT (fig. 1). CC-PT and LAB-PT correlation values (r^2) were 0.24, 0.30 and 0.71 in groups A, B and C, respectively (fig. 2). Expression of PT as INR (logarithmic scale) did not improve the correlation between CC-PT and LAB-PT, with r^2 values of 0.12, 0.12 and 0.73 for groups A, B and C, respectively. Extreme outliers in group A and B are apparent in figures 1 and 2.

There was no trend in the accuracy between measurements before, during and after operation for all groups. Furthermore, accuracy was similar for normal (PT <13.5 s) and abnormal (PT ≥13.5 s) ranges of PT. Most of the abnormal PT values were found in group B.

Discussion

We found only a weak correlation between prothrombin time measured with the CoaguChek-Plus monitor and that measured in the laboratory. Several outliers contributed substantially to the poor accuracy of the device. In several cases the difference in LAB-PT and CC-PT was 10–16 s. Thus the CoaguChek-Plus monitor indicated an abnormal PT when a normal PT was verified by standard laboratory testing and clinical judgement. These false pathological PT values may lead to unnecessary and potentially harmful substitution therapy with blood products. There were no outliers in group C, but the probability of outliers occurring was limited because of the low number of comparisons (16 *vs* 138 and 37 for groups A and B, respectively). Accordingly, the best correlation was found in this group. The poor accuracy of the device was found equally for measurements before, during and after operation, and for different ranges of PT.

In view of the small number of outliers, it might be

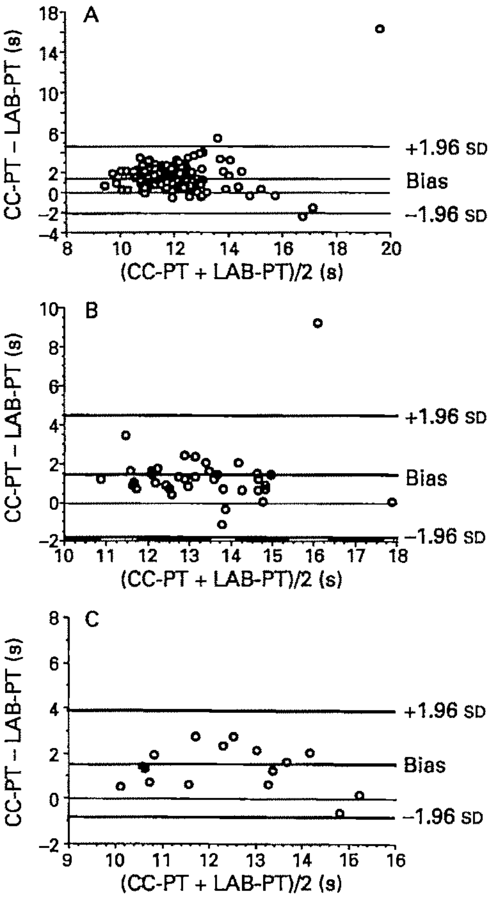

Figure 1 Bland Altman plot showing bias (mean of differences) and precision (1.96 SD of these differences) of prothrombin time obtained by the CoaguChek-Plus monitor (CC-PT) compared with prothrombin time measured with standard laboratory assays (LAB-PT) in group A (n=138; A), group B (n=37; B) and group C (n=16, C), respectively.

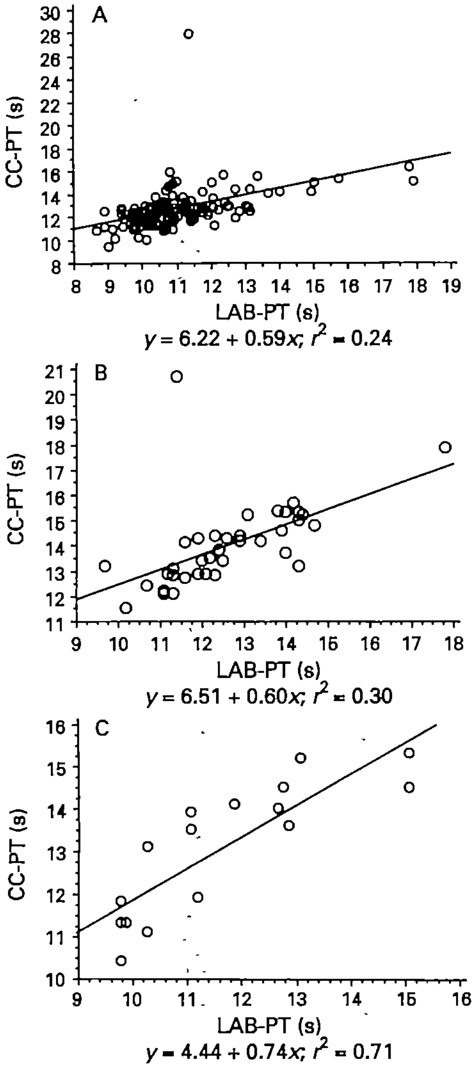

Figure 2 Equations of regression lines and plots of linear regression showing prothrombin time measured using standard laboratory assays (LAB-PT) compared with prothrombin time obtained by the CoaguChek-Plus monitor (CC-PT) for groups A (A), B (B) and C (C).

argued that technical or handling errors may have been responsible for inaccurate measurements. However, blood sampling, measurements and calibration were performed carefully by the investigators in strict accordance with the recommendations of the manufacturer. Moreover, in daily clinical practice, an on-site coagulation monitor should be easily and reliably used by theatre staff.

The accuracy of measurement of PT with the CoaguChek-Plus coagulation monitor has been validated in a wide range of medical specialities, such as clinical pathology,[7–9] haematology,[10] cardiac surgery[2–5] and gynaecological surgery.[6] Most studies showed acceptable accuracy in comparison with standard laboratory methods., Jennings, Luddington and Baglin evaluated the CoaguChek-Plus for the control of oral anticoagulation.[8] They compared several thromboplastins, including lyophilized rabbit brain thromboplastin used in the CoaguChek-Plus monitor with the "consensus" (mean of all compared INR) within the therapeutic range for oral anticoagulation. The results showed a clinically and statistically significant overestimation by the CoaguChek-Plus monitor. The authors concluded that the CoaguChek-Plus would be suitable for decentralized anticoagulant monitoring, but should not be used when laboratory testing with standard thromboplastin is available.

The international sensitivity index (ISI), which has a logarithmic relationship to INR, describes the individual sensitivity of a thromboplastin compared with the WHO (World Health Organisation) reference thromboplastin. Tripodi and colleagues determined the ISI and precision of the INR of the CoaguChek-Plus monitor compared with the secondary international WHO reference preparation for rabbit thromboplastin.[10] ISI was 2.715, which is higher than that adopted by the manufacturer (2.036), and also higher than the laboratory thromboplastin of our study (0.96). The authors suggested that the poor correlation of INR may be caused by the high ISI. They also recommended the use of more sensitive thromboplastins with lower ISI values because these show smaller between-laboratory variability. This argument may also explain the worsening of the correlation we found in groups A and B after expressing PT as INR units. Nevertheless, for comparison of PT values, INR is the only relevant parameter.[11 12] In accordance with Tripodi and colleagues, we would prefer a more sensitive thromboplastin for on-site PT measurement.

Despotis and colleagues[3] and Reich and colleagues[5] reported an acceptable accuracy for the CoaguChek-Plus monitor in cardiac surgery compared with laboratory standard assays. Samama and colleagues also found good correlations in vascular and gynaecological surgery.[6] In contrast, Nuttal and colleagues found only moderate correlation with laboratory assays in their study of 100 patients undergoing cardiopulmonary bypass.[4] These authors concluded that "speeding access" to hospital laboratory results would be a more efficacious alternative.

In contrast with previous work, we performed repeated measurements in individual patients. Furthermore, the reliability of the CoaguChek-Plus monitor was evaluated under various haemostatic conditions. Its accuracy may suffice for the control of oral anticoagulation,[7–9] but our results indicate that CoaguChek-PT measurements are not reliable enough for clinical decision making in non-cardiac surgery.

During elective aortic replacement surgery, even laboratory PT has been shown to be unreliable for assessing coagulation status.[13] Within the past decade, thrombelastography has become a useful adjunct to intraoperative haemostasis management, enabling a global assessment of haemostatic function.[14] Together with the processes of clot formation, clot strengthening and clot lysis, even platelet function can be determined.[15 16] The various thrombelastographic variables correlate closely with intraoperative coagulopathy and enable selective substitution of blood products in accordance with the specific requirements of the case.[17] If indicated, an accurate platelet count may also be obtained on-site.[3]

In summary, we advise against the use of the CoaguChek-Plus coagulation monitor to evaluate the patient's prevailing prothrombin time or to monitor changes during non-cardiac surgery. The associated time-saving effect does not compensate for the lack of reliability. Perioperative haemostasis management should be based primarily on good clinical judgement and reliable coagulation testing, such as is provided by laboratory coagulation status, when indicated in combination with on-site platelet count, on-site activated clotting time or thrombelastography.[13 14–16]

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References

1. Wong CA. Coagulation testing. *Current Opinion in Anesthesiology* 1996; 9: 495–498.
2. Despotis GJ, Santoro SA, Spitznagel E, Kater KM, Cox JL, Barnes P, Lappas DG. Prospective evaluation and clinical utility of on-site coagulation monitoring in cardiac surgical patients. *Journal of Thoracic and Cardiovascular Surgery* 1994; 107: 271–279.
3. Despotis GJ, Santoro SA, Spitznagel E, Kater KM, Barnes B, Cox JL, Lappas DG. On-site prothrombin time, activated partial thromboplastin time and platelet count. A comparison between whole blood and laboratory assays with coagulation factor analysis in patients presenting for cardiac surgery. *Anesthesiology* 1994; 80: 338–351.
4. Nuttall GE, Oliver WC, Beynen FM, Dull JJ, Murray MJ, Nichols WL. Intraoperative measurement of activated partial thromboplastin time and prothrombin time by a portable laser photometer in patients after cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia* 1993; 7: 402–409.
5. Reich DL, Yananakis MJ, Vela-Cantos FP, DePerio M, Jacobs E. Comparison of bedside coagulation monitoring tests with standard laboratory tests in patients after cardiac surgery. *Anesthesia and Analgesia* 1993; 77: 673–679.
6. Samama CM, Quezada R, Riou B, Mourgeon E, Arock M, Viars P. Intraoperative measurement of activated partial thromboplastin time and prothrombin time with a new compact monitor. *Acta Anaesthesiologica Scandinavica* 1994; 38: 232–237.
7. Lucas FV, Duncan A, Jay R, Coleman R, Craft P, Chan B, Winfrey L, Mungall DR, Hirsh J. A novel whole blood capillary technique for measuring the prothrombin time. *American Journal of Clinical Pathology* 1987; 88: 442–446.
8. Jennings I, Luddington RJ, Baglin T. Evaluation of the Ciba Corning Biotrack 512 coagulation monitor for the control of oral anticoagulation. *Journal of Clinical Pathology* 1991; 44: 950–953.
9. Dehara K, Yoshiba M, Inoue K, Sugata F. A simple method for evaluating prothrombin time in severe liver disease. *American Journal of Clinical Pathology* 1994; 101: 358–360.
10. Tripodi A, Arbini AA, Chantarangkul V, Bettega D, Mannucci PM. Are capillary whole blood coagulation monitors suitable for the control of oral anticoagulant treatment by the international normalized ratio? *Thrombosis and Haemostasis* 1993; 70: 921–924.
11. Loeliger EA, Van den Besselaar AMHP, Lewis SM. Reliability and clinical impact of the normalization of the prothrombin times in oral anticoagulant control. *Thrombosis and Haemostasis* 1985; 53: 148–154.
12. Loeliger EA, Poller L, Samama M, Thomson JM, Van den Besselaar AMHP, Vermylen J, Verstraete M. Questions and answers on prothrombin time standardisation in oral anticoagulant control. *Thrombosis and Haemostasis* 1985; 54: 515–517.
13. Vahl AC, Mackaay AJC, Huijgens PC, Scheffer GJ, Rauwerda JA. Haemostasis during infrarenal aortic aneurysm surgery: effect of volume loading and cross clamping. *European Journal of Vascular and Endovascular Surgery* 1997; 13: 60–65.
14. Kang YG, Martin DJ, Marquez JM, Lewis JH, Bontempo FH, Shaw BW, Starzl TE, Winter PM. Intra-operative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. *Anesthesia and Analgesia* 1985; 64: 888–896.
15. Mallett SV, Cox DJA. Thrombelastography. *British Journal of Anaesthesia* 1992; 69: 307–313.
16. Caprini JA, Traverso C, Walenga J, Arcelus J, Fareed J, Spiess B. Thromboelastography. *Seminars in Thrombosis and Hemostasis* 1995; 21 (Suppl. 4): 1–93.
17. Spiess BD, Gillies BSA, Chandler W, Verrier W. Changes in transfusion therapy and reexploration rate after institution of a blood management program in cardiac surgical patients. *Journal of Cardiothoracic and Vascular Anesthesia* 1995; 9: 168–173.

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Laryngeal mask airway and incidence of gastro-oesophageal reflux in paralysed patients undergoing ventilation for elective orthopaedic surgery

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Summary

We have studied the incidence of gastro-oesophageal reflux associated with the laryngeal mask airway (LMA) in 82 paralysed patients undergoing ventilation for elective orthopaedic surgery. Anaesthesia was managed by skilled LMA users. A pH-sensitive probe was passed nasally into the oesophagus before induction and recordings made during five phases of anaesthesia. Anaesthesia was induced with propofol and fentanyl and maintained with 0.5–1.5% isoflurane and nitrous oxide in oxygen. Neuromuscular block was produced with vecuronium and the train-of-four count maintained at ≤1. Towards the end of surgery, neuromuscular function was allowed to recover spontaneously. All LMAs were inserted at the first attempt and ventilation was successful in all patients. There were no adverse airway events. Mean oesophageal pH values during each phase of anaesthesia were: before insertion 5.88 (SD 0.77), placement 5.85 (0.74), maintenance 5.89 (0.73), emergence 5.71 (0.78) and removal 5.82 (0.75). There were no reflux events (pH <4.0) during any phase of anaesthesia. We conclude that the incidence of gastro-oesophageal reflux is low in paralysed patients undergoing ventilation for elective orthopaedic surgery when antagonism of neuromuscular block is avoided. The validity of these findings for unskilled LMA users is unknown. (*Br. J. Anaesth.* 1998; **81**: 537–539).

Keywords: gastrointestinal tract, pH; gastrointestinal tract, reflux, equipment, masks anaesthesia; surgery, orthopaedic

The laryngeal mask airway (LMA) has gained widespread popularity as a general purpose airway and has some advantages over the tracheal tube and face mask.[1] A limiting factor with the use of the LMA is the lack of airway protection from regurgitated gastric contents,[2] and some practitioners consider that the presence of the device in the pharynx could promote regurgitation.[3] Published data have provided conflicting results, with a reported incidence of gastro-oesophageal reflux of 0–80%.[4–10] In this study, we have determined the incidence of gastro-oesophageal reflux associated with the LMA in paralysed patients undergoing ventilation for elective orthopaedic surgery.

Patients and methods

After obtaining approval from the Hospital Ethics Committee and written informed consent, we studied 82 consecutive adult patients, ASA I–III, undergoing elective orthopaedic surgery at the University School of Medicine LIU Campus Bio-Medico, Rome, Italy. Patients were excluded if they were <18 yr, required surgery in non-supine positions, had a body mass index (BMI) >35 kg m^{-2}, were at risk of aspiration (previous upper gastrointestinal tract surgery, known or symptomatic hiatus hernia, oesophageal reflux, peptic ulceration or not fasted) or were considered otherwise unsuitable for an LMA. Patients receiving antacid therapy or drugs affecting gastrointestinal motility were excluded. All investigators were experienced with the LMA (>200 uses and first-time failure rate <5%).

Premedication comprised midazolam 0.04 mg kg^{-1} i.v., approximately 30 min before induction. A monocrystalline antimony pH electrode (Zinetics Medical Inc, Salt Lake City, UT, USA) was placed in the stomach via the nose before induction of anaesthesia. Intragastric position was confirmed by the presence of a low pH. The electrode (2 mm) was then positioned in the lower oesophagus by withdrawing it slowly until a higher pH was obtained (pH 5–6). A flexilog 1011 pH data logger system/monitor (Oakfield Instruments Ltd, Oxford, UK) recorded pH every 6 s and displayed the information continuously on a visible liquid crystal display screen. Before and after each use, the electrode was adjusted in buffer solution at pH 4 and pH 7, 37°C. Any decrease in pH to <4.0 was deemed to indicate gastro-oesophageal reflux.[8 10] Data from the data logger were downloaded to a computer for further analysis.

Standard monitoring was applied, including an ECG, pulse oximeter, capnograph and non-invasive arterial pressure monitor. A TOF guard accelerometer (Biometer Int., Odense, Denmark) was used to quantify neuromuscular block. Patients were preoxygenated for 2 min, and then fentanyl 5 μg kg^{-1} i.v. was given followed 1 min later by propofol 3 mg kg^{-1} i.v. over 30 s. Patients' lungs were ventilated by face

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mask for 30 s with 100% oxygen. The LMA was inserted using the standard technique[11] when the eyelash reflex was lost, the jaw was relaxed and the patient apnoeic. Additional bolus doses of propofol 0.5 mg kg^{-1} i.v. were given as required until an adequate level of anaesthesia was achieved for placement of the LMA. Anaesthesia was maintained with 0.5–1.5% isoflurane and 67% nitrous oxide in oxygen.

A size 4 LMA was used for small adults (<60 kg) and a size 5 for large adults (≥60 kg). The LMA cuff was inflated with air until an effective seal was formed or up to the maximum recommended volume (30 ml, size 4; 40 ml, size 5). Adequate ventilation was judged by chest wall movement, capnography and an airway sealing pressure[12] ≥10 cm H_2O during manually assisted ventilation. If adequate ventilation was not possible, the LMA was removed and a different size inserted. After insertion of the LMA, the position of the probe was verified to ensure that it had not migrated distally. A rolled gauze swab was inserted as a bite block and the LMA fixed in place in the midline using adhesive tape with the tube following its natural caudal curve. When adequate ventilation was established, patients were given vecuronium 0.1 mg kg^{-1} and neuromuscular block was maintained using increments of 0.03 mg kg^{-1} if the train-of-four count was >1. Patients underwent positive pressure ventilation (Ohmeda 210 Excel, Ohmeda Inc., Madison, USA) with tidal volumes of 8 ml kg^{-1}; peak airway pressure was <20 cm H_2O. Ventilatory frequency was adjusted to maintain PE'_{CO_2} in the normal range (4.3–4.7 kPa). Epigastric stethoscopy was performed for 1 min during maintenance of anaesthesia to detect any air entering the stomach. Towards the end of surgery, neuromuscular function was allowed to recover spontaneously and anaesthesia was discontinued when the train-of-four ratio was >0.7. Patients underwent manually assisted ventilation until spontaneous breathing resumed. The LMA was removed when the patient was able to open their mouth to command.

Failed positive pressure ventilation was defined as Sa_{O_2} <95% with an FI_{O_2} of 0.33 or PE'_{CO_2} >4.7 kPa. Any adverse airway events, such as a change in patient position, coughing, hiccups, gagging or bucking were noted and timed. All pH data were analysed independently by two investigators. Gastro-oesophageal reflux was observed and analysed during five consecutive phases of anaesthesia: (1) pre-insertion phase (placement of probe to commencement of insertion of the LMA); (2) placement phase (insertion of the LMA to establishment of an effective airway); (3) maintenance phase (effective airway to discontinuation of anaesthesia); (4) emergence phase (discontinuation of anaesthesia until removal of the device); and (5) removal phase (removal of device until removal of pH probe).

Results

Mean age, height, weight, body mass index and duration of surgery were 42 (range 21–81) yr, 165 (SD 9, range 148–181) cm, 70 (13, 43–105) kg, 25.7 (4.4, 19–35) kg m^{-2} and 50 (20, 22–184) min, respectively. All LMAs were inserted at the first attempt and ventilation was successful in all patients. There were no adverse airway events in any patient and gastric insufflation was not detected. Mean preoperative gastric pH was 2.5 (SD 0.32). Mean oesophageal pH values during each phase of anaesthesia were: before insertion 5.88 (SD 0.77, range 4.1–6.8), placement 5.85 (0.74, 4.3–6.8), maintenance 5.89 (0.73, 4.2–6.5), emergence 5.71 (0.78, 4.0–6.8) and removal 5.82 (0.75, 4.1–6.6). There were no reflux events during any phase of anaesthesia.

Discussion

Our data suggest that the incidence of gastro-oesophageal reflux is low in paralysed patients undergoing ventilation for elective orthopaedic surgery. Assuming a binomial distribution for the number of regurgitations, the upper limit for the probability when no cases have been observed in 82 patients is 0.046.[13] Therefore, we can state with 95% confidence that the true rate of gastro-oesophageal reflux is <4.6%.

Valentine, Stakes and Bellamy, who studied 10 paralysed patients undergoing ventilation with an oesophageal pH probe, reported gastro-oesophageal reflux in 40% of patients, increasing to 80% during antagonism of neuromuscular block.[9] This was attributed to possible gastric insufflation. A recent study by Bapat and Verghese of 100 paralysed patients undergoing ventilation for gynaecological laparoscopy reported no hypopharyngeal reflux events when managed by experienced LMA users, even in patients at risk of regurgitation.[10] One reason for the lower incidence of reflux may have been that pH was measured in the hypopharynx; thus reflux events in the upper oesophagus may have been undetected. The differences may also be related to the definition of reflux: Valentine, Stakes and Bellamy considered a discrete pH change of 1 or more units, or an absolute decrease to less than 5, to be indicative of reflux, whereas Bapat and Verghese selected an absolute decrease below 4. However, it has also been suggested that the high incidence of reflux in the study of Valentine, Stakes and Bellamy may have been caused by inadequate depth of anaesthesia, premature antagonism of neuromuscular block and inexperience with the LMA.[14] It has been shown that most episodes of gastro-oesophageal reflex during anaesthesia are related to the conduct of anaesthesia and occur during coughing or bucking.[15 16] There is both a short-[17] and long-term[18] learning curve with the LMA. In our study, all anaesthetists were experienced and skilled in the use of the LMA, and there were no episodes of coughing or bucking. It is not known if avoidance of antagonism of neuromuscular block contributed to the low incidence of gastro-oesophageal reflux in our series. Although Valentine, Stakes and Bellamy reported a high incidence of reflux events during antagonism, Bapat and Verghese reported no reflux events at that time.

In summary, our data suggests that the incidence of gastro-oesophageal reflux is low in paralysed patients undergoing ventilation for elective orthopaedic surgery when antagonism of neuromuscular block is avoided. The validity of these findings for unskilled LMA users is unknown.

References

1. Brimacombe J. The advantages of the LMA over the tracheal tube or facemask: a meta-analysis. *Canadian Journal of Anaesthesia* 1995; **42**: 1017–1023.

2. Brimacombe J, Berry A. The incidence of aspiration associated with the laryngeal mask airway—a meta-analysis of published literature. *Journal of Clinical Anesthesia* 1995; 7: 297–305.
3. Rabey PG, Murphy PJ, Langton JA, Barker P, Rowbotham DJ. Effect of the laryngeal mask airway on lower oesophageal sphincter pressure in patients during general anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 346–348.
4. Joshi GP, Morrison SG, Okonkwo NA, White PF. Continuous hypopharyngeal pH measurements in spontaneously breathing anesthetised outpatients: laryngeal mask airway versus tracheal intubation. *Anesthesia and Analgesia* 1996; **82**: 254–257.
5. Akhtar TM, Street MK. Risk of aspiration with the laryngeal mask. *British Journal of Anaesthesia* 1994; 72: 447–450.
6. Barker P, Langton JA, Murphy PJ, Rowbotham DJ. Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway. *British Journal of Anaesthesia* 1992; **69**: 314–315.
7. El Mikatti N, Luthra AD, Healy TEJ, Mortimer AJ. Gastric regurgitation during general anaesthesia in different positions with the laryngeal mask airway. *Anaesthesia* 1995; **50**: 1053–1055.
8. Owens TM, Robertson P, Twomey C, Doyle M, McDonald N, McShane AJ. The incidence of gastroesophageal reflux with the laryngeal mask: a comparison with the facemask using esophageal lumen pH electrodes. *Anesthesia and Analgesia* 1995; **80**: 980–984.
9. Valentine J, Stakes AF, Bellamy MC. Reflux during positive pressure ventilation through the laryngeal mask. *British Journal of Anaesthesia* 1994; 73. 543–545.
10. Bapat P, Verghese C. Laryngeal mask airway and the incidence of regurgitation during gynecological laparoscopies. *Anesthesia and Analgesia* 1997; **85**: 139–143.
11. Brimacombe J, Brain AIJ, Berry A. *The Laryngeal Mask Airway Instruction Manual.* Henley-on-Thames: Intavent Research Ltd, 1996.
12. Epstein RH, Ferouz F, Jenkins MA. Airway sealing pressures of the laryngeal mask airway in pediatric patients. *Journal of Clinical Anesthesia* 1996; **8**: 93–98.
13. Pearson ES, Hartley HO, eds. *Biometric Tables for Statisticians* Cambridge: Cambridge University Press, 1970; 228.
14. Brain AIJ, Brimacombe J, Berry A, Verghese C. Reflux during positive pressure ventilation through the laryngeal mask airway? *British Journal of Anaesthesia* 1995; 74: 489–490.
15. Illing L, Duncan PG, Yip R. Gastro-oesophageal reflux during anaesthesia. *Canadian Journal of Anaesthesia* 1992; **39**: 466–470.
16. Hardy JF, Lepage Y, Bonneville Chouinard N Occurrence of gastroesophageal reflux on induction of anaesthesia does not correlate with the volume of gastric contents. *Canadian Journal of Anaesthesia* 1990; 37: 502–508.
17. Lopez-Gil M, Brimacombe J, Cebrian J, Arranz J. The laryngeal mask airway in pediatric practice—a prospective study of skill acquisition by resident anesthesiologists. *Anesthesiology* 1996; **84**: 807–811.
18. Brimacombe J. Analysis of 1500 laryngeal mask uses by one anaesthetist in adults undergoing routine anaesthesia. *Anaesthesia* 1996; **51**: 76–80

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Assessment of intubating conditions in adults after induction with propofol and varying doses of remifentanil

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Summary

We have assessed intubating conditions in three groups of 60 ASA I or II patients after induction of anaesthesia with propofol 2 mg kg^{-1} and remifentanil 0.5, 1.0 or 2.0 μg kg^{-1}. Tracheal intubation was graded according to ease of laryngoscopy, position of the vocal cords, coughing, jaw relaxation and movement of the limbs. Intubation was successful in 80%, 90% and 100% of patients after remifentanil 0.5, 1.0 or 2.0 μg kg^{-1}, respectively. Overall intubating conditions were regarded as acceptable in 20%, 50% and 80% of patients, respectively. All three groups had a decrease in arterial pressure after induction but there was no difference between groups. The decrease in arterial pressure was not regarded as clinically significant. Intubating conditions were best after induction with remifentanil 2 μg kg^{-1} and propofol 2 mg kg^{-1}. (*Br. J. Anaesth.* 1998; **81**: 540–543).

Keywords: analgesics opioid, remifentanil; anaesthetics i v, propofol; intubation tracheal

The use of propofol and adjuvants such as short-acting opioids, adrenergic blockers and local anaesthetic agents, may provide adequate conditions for laryngoscopy and tracheal intubation without the need for neuromuscular blocking agents.[1–4] Previous work in premedicated adults showed that tracheal intubation was successful after induction of anaesthesia with alfentanil and propofol and conditions were similar to those achieved with thiopental (thiopentone) and succinylcholine (suxamethonium).[5] Given the pharmacokinetic profile of remifentanil, it was hypothesized that it may also be useful in facilitating tracheal intubation.

After a small pilot study, we designed a prospective, randomized, double-blind study to assess intubating conditions and haemodynamic changes in three groups of premedicated adults. Three doses of remifentanil (0.5, 1.0 and 2.0 μg kg^{-1}) supplementing induction of anaesthesia with propofol 2 mg kg^{-1} were compared.

Patients and methods

After obtaining approval from the Ethics Committee and written informed consent, we studied 60 ASA I or II patients undergoing elective inpatient surgery. Patients whose physical characteristics suggested difficulties in intubation (modified Mallampati score III or IV)[6] and those who had a previously documented failed intubation were excluded. Patients with a history of reactive airways disease, including asthma, and a history of upper gastrointestinal reflux were also excluded. All patients were premedicated with temazepam 20–30 mg and ranitidine 150 mg approximately 1 h before anaesthesia.

On arrival in the anaesthetic room, an 18-gauge cannula was inserted into a peripheral vein, non-invasive arterial pressure, electrocardiogram (ECG) and pulse oximeter (Sp_{O_2}) were attached, and baseline measurements were recorded (pre-induction). Patients were preoxygenated while these variables were recorded. Patients were allocated randomly (using a computer program) before commencement of the study to one of three groups: group I=propofol 2 mg kg^{-1} and remifentanil 0.5 μg kg^{-1}; group II=propofol 2 mg kg^{-1} and remifentanil 1 μg kg^{-1}; and group III=propofol 2 mg kg^{-1} and remifentanil 2 μg kg^{-1}. Assignment to each group was concealed using sealed envelopes. The envelope was opened and remifentanil was prepared by anaesthetist No. 1. The remifentanil solution was diluted to a volume of 10 ml with 0.9% saline. Remifentanil was administered as a slow bolus infusion over 30 s. When the bolus dose of remifentanil was given, propofol 2 mg kg^{-1} was administered as a rapid i.v. bolus by hand-held syringe. When the patient lost consciousness, which was judged by loss of response to command and loss of eyelash reflex, ventilation via a mask was attempted by anaesthetist No. 2 (always J. A. D., who was blinded to the randomization group).

Ease of ventilation was recorded as easy, difficult or impossible. Vital signs were measured 45 s after the bolus dose of propofol (post-induction). If the dose of propofol was not sufficient to produce loss of consciousness, as determined by anaesthetist No. 2, further propofol was titrated in incremental boluses of 20 mg until this was achieved. Ninety seconds after propofol was administered, laryngoscopy was attempted by anaesthetist No. 2. During laryngoscopy and attempted intubation of the trachea, the anaesthetist performing intubation assessed each patient for one of five variables: jaw relaxation, exposure of the vocal cords, position of the vocal cords, patient movement and coughing. The criteria used for ranking these variables are shown in table 1. This

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Table 1 Intubating condition score

	Score			
	1	2	3	4
Jaw relaxation	Complete	Slight tone	Stiff	Rigid
Laryngoscopy	Easy	Fair	Difficult	Impossible
Vocal cords	Open	Moving	Closing	Closed
Coughing	None	Slight	Moderate	Severe
Limb movement	None	Slight	Moderate	Severe

Table 2 Patient data (mean (SD or range) or number)

	Group I	Group II	Group III
Sex (m/f)	10 / 10	5 /15	5 /15
Age (yr)	46 100–00	45 100–00	47 100–00
Weight (kg)	75 (16.2)	72 (16.8)	71 (13)

is a modification of the scoring system described by Helbo-Hansen, Ravlo and Trap-Andersen.[7] One attempt was allowed at laryngoscopy, and assessment of all variables was made from this attempt. Intubating conditions were judged as acceptable when all scores were 2 or less. If any of the scores were 3 or 4 for any of the five variables, intubating conditions were judged unfavourable. Patients in whom intubation was impossible were given rocuronium 600 μg kg^{-1} to optimize conditions. Vital signs were recorded (post-intubation). In the event of bradycardia (heart rate less than 50 beat min^{-1}), atropine 500 μg was administered. In the event of a decrease in mean arterial pressure of greater than 25%, ephedrine was administered in 6-mg increments. Anaesthesia was maintained at the discretion of the anaesthetist in charge.

STATISTICAL ANALYSIS

Parametric data were analysed using analysis of variance. A change in arterial pressure or heart rate >20% was regarded as a clinically significant difference. Chi-square analysis was applied to non-parametric data and Bonferroni correction to multiple comparisons. $P<0.05$ was regarded as significant.

Results

We studied 60 adults in three groups of equal size. The three groups were comparable in age and weight (table 2).

Because 50% of the operating sessions were gynaecological, there was a predominance of female subjects (40 females, 20 males). Intubation was completed successfully in 54 of 60 patients using propofol and remifentanil alone (16 of 20 in group I, 18 of 20 in group II and 20 of 20 in group III). One subject in group I required rocuronium. Additional propofol only (20–80 mg) was required in five subjects in group I. Additional propofol and rocuronium were required in three subjects in group I and in two subjects in group II. All subjects given additional propofol, neuromuscular blocking drug, or both, were subsequently intubated successfully. Subjects who required additional propofol or a neuromuscular blocking agent were defined as having unacceptable intubating conditions. Individual assessment of jaw relaxation, view at laryngoscopy, vocal cord position, limb movement and coughing improved significantly as the dose of remifentanil was increased (fig. 1).

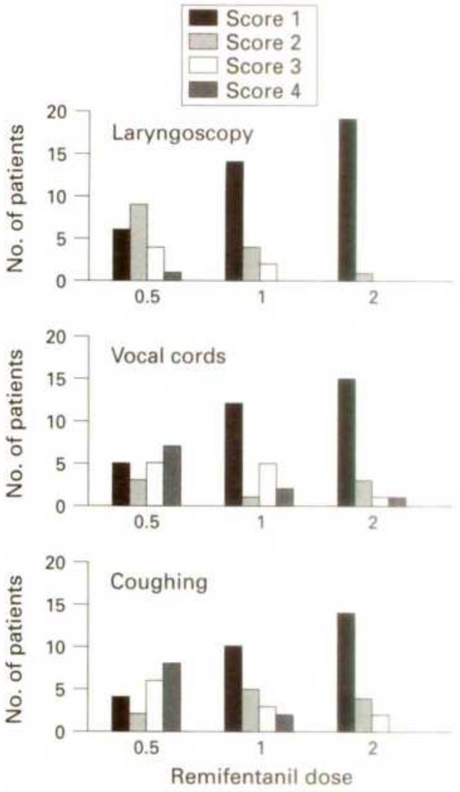

Figure 1 Intubating condition score for laryngoscopy, vocal cords and coughing in patients in each group: 0.5=Remifentanil 0.5 μg kg^{-1} and propofol 2 mg kg^{-1}; 1=remifentanil 1.0 μg kg^{-1} and propofol 2 mg kg^{-1}; and 2=remifentanil 2.0 μg kg^{-1} and propofol 2 mg kg^{-1}.

Muscle rigidity or difficulty with ventilation was not found to be a problem in any of the 60 subjects. Overall assessment for all five variables at intubation is shown in figure 2. A score of 2 or less for all of the criteria in table 1 was deemed as satisfactory intubating conditions. A score of 3 or greater for any of the criteria was categorized as unsatisfactory. Only four of 20 subjects (20%) in group I were judged to have satisfactory intubating conditions compared with 10 of 20 (50%) in group II and 16 of 20 (80%) in group III. There was a statistically significant difference in overall intubation conditions between groups I, II and III ($P<0.05$).

Cardiovascular responses to induction and intubation are shown in figure 3. The initial haemodynamic

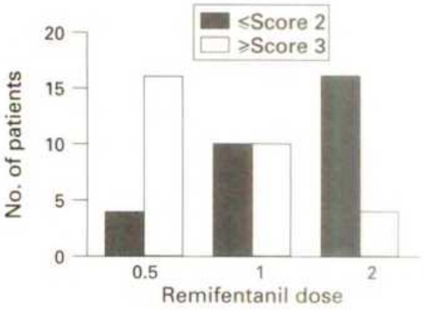

Figure 2 Overall intubating conditions in patients in the three groups. All scores of ≤2=acceptable intubating conditions while any score ≥3=unacceptable intubating conditions. 0.5=Remifentanil 0.5 μg kg^{-1} and propofol 2 mg kg^{-1}; 1=remifentanil 1.0 μg kg^{-1} and propofol 2 mg kg^{-1}; and 2=remifentanil 2.0 μg kg^{-1} and propofol 2 mg kg^{-1}.

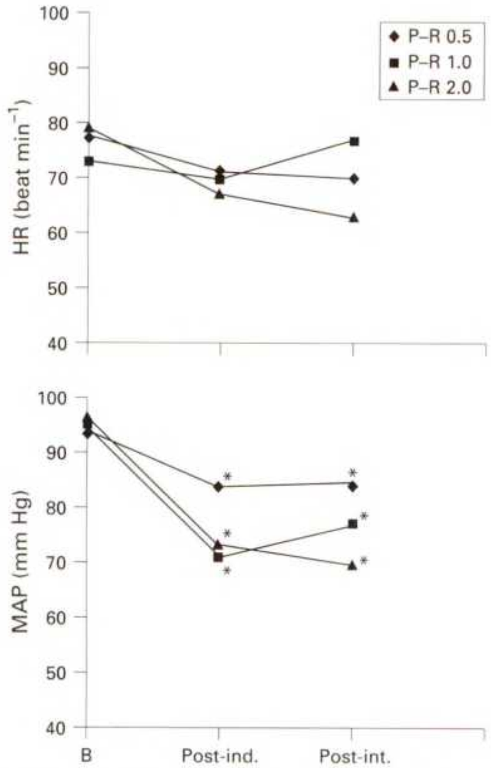

Figure 3 Heart rate (HR) and arterial pressure (MAP) responses to laryngoscopy and intubation after propofol–remifentanil 0.5 μg kg^{-1} (P–R 0.5), propofol–remifentanil 1.0 μg kg^{-1} (P–R 1.0) and propofol–remifentanil 2.0 μg kg^{-1} (P–R 2.0). Within-group significant changes compared with values before induction: *$P<0.05$. B= Baseline; Post-ind.=after induction; Post-int.=after intubation.

variables were similar in the three groups. There was a decrease in heart rate after induction in all three groups but this was not clinically or statistically significant. No patient required atropine. The decrease in arterial pressure after induction and intubation in all three groups was statistically significant compared with baseline, but was not regarded as clinically significant. There were no significant differences in arterial pressures between groups at any time. Two patients in group III were given ephedrine.

Discussion

Our data demonstrated that tracheal intubation was possible in premedicated adults with favourable airway anatomy after i.v. induction with remifentanil and propofol. In combination with propofol 2 mg kg^{-1}, the best conditions achieved in this study were with remifentanil 2 μg kg^{-1}.

Previous studies have concluded that intubation is possible without the use of neuromuscular blocking agents. Using only propofol 2.5 mg kg^{-1}, Keaveney and Knell[1] reported satisfactory intubating conditions in 12 of 20 patients. Saarnivaara and Klemola[2] assessed various doses of alfentanil in premedicated adult patients and produced successful intubation in 86% of patients using alfentanil 30 μg kg^{-1} and propofol 2.5 mg kg^{-1}. A similar success rate was reported by Coghlan, McDonald and Csepregi who studied unpremedicated adults and achieved successful intubation in 83% of patients using alfentanil 20 μg kg^{-1} and propofol 2.5 mg kg^{-1}.[3] Scheller, Zornow and Saidman[5] studied 75 patients (group I received tubocurarine 3 mg, thiopental 4 mg kg^{-1} and succinylcholine 1 mg kg^{-1} and groups II–V alfentanil 30, 40, 50 or 60 μg kg^{-1} combined with propofol 2 mg kg^{-1}). They concluded that in premedicated patients with favourable airway anatomy receiving alfentanil 40 μg kg^{-1} and propofol for induction, intubating conditions and patient response to intubation differed little from those achieved with thiopental and succinylcholine.

Remifentanil is 20–25 times more potent than alfentanil. If our results are compared with the equally potent alfentanil 40 μg kg^{-1} group in Scheller's study, remifentanil 2 μg kg^{-1} combined with propofol is comparable in terms of intubation and haemodynamic response. It has been suggested by Steyn and colleagues[8] that by aiming for a defined clinical end-point at induction of anaesthesia rather than fixing the dose of propofol at 2 mg kg^{-1}, it might be possible to improve intubating conditions further and reduce side effects such as hypotension. However, even with the fixed dose of propofol in our study, the mean decrease in arterial pressure was not clinically significant. But we would add a caution to the use of this technique in the elderly or compromised patient. The decrease in arterial pressure which was compensated for by the reasonably healthy subjects in our study might not be as well tolerated in less healthy patients. The need for dose reduction in the elderly or compromised patient is an area of further study. A small percentage of patients in this study experienced coughing after intubation but this did not interfere with passage of the tracheal tube.

The effects of remifentanil are short acting,[9] and timing to achieve the maximum effect of the combination of propofol and remifentanil is important. Using a computerized pharmacokinetic model, we determined that peak blood concentrations would be approximately 6 ng ml^{-1} and that these would be achieved at approximately 90 s after our 30-s infusion of remifentanil 2 μg kg^{-1}.

The short duration of action of remifentanil may confer an advantage over alfentanil where there are problems with prolonged apnoea in short surgical cases.[5] Metabolism of alfentanil has been shown to be very variable.[10] It is dependant on cytochrome P450 A34 and there is large inter-individual variation in the activity of this enzyme. Remifentanil is metabolized by non-specific tissue esterases and has a reliable context-sensitive half-life of approximately 3 min.[11] This short half-life is not relevant however, if remifentanil and propofol are supplemented rapidly by inhalation anaesthetics after intubation.

In the event of a prolonged difficult intubation which is predicted or, more importantly, unexpected, we feel this technique is advantageous. It allows assessment of the airway by laryngoscopy and also importantly if oxygenation is possible. The decision whether or not to awaken the patient or proceed can then be made.

The reliably short duration of apnoea is the main advantage of remifentanil compared with alfentanil. We note from our clinical experience with this technique that the duration of apnoea is similar to that with succinylcholine. The design of this dose-finding study made it impossible to assess the duration of apnoea scientifically and a follow-on study examining this is underway.

We see a potential use for this technique in ENT and gynaecological anaesthesia and in any case where intubation is necessary but neuromuscular block is not required to facilitate surgical access. We also see potential use in cases where neuromuscular blocking agents are contraindicated (e.g. myopathies) or where succinylcholine is contraindicated but a rapid sequence technique is required (e.g. hyperkalaemia, burns, plasma cholinesterase deficiency or penetrating eye injury).

References

1. Keaveney J, Knell P. Intubation under induction doses of propofol. *Anaesthesia* 1988; **43S**: 80–81.
2. Saarnivaara L, Klemola U. Injection pain, intubating conditions and cardiovascular changes following induction of anaesthesia with propofol alone or in combination with alfentanil. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 19–23.
3. Coghlan S, McDonald P, Csepregi G. Use of alfentanil with propofol for nasaltracheal intubation without neuromuscular block. *British Journal of Anaesthesia* 1993; **70**. 89–91
4. Davidson J, Gillespie J. Tracheal intubation after induction of anaesthesia with propofol, alfentanil and i.v. lignocaine. *British Journal of Anaesthesia* 1993; **70**: 163–166.
5. Scheller M, Zornow M, Saidman L. Tracheal intubation without the use of muscle relaxants: A technique using propofol and varying doses of alfentanil. *Anesthesia and Analgesia* 1992, **75**· 788–793.
6. Samsoon G, Young J. Difficult tracheal intubation a retrospective study. *Anaesthesia* 1987; **42**: 487–490.
7. Helbo-Hansen S, Ravlo O, Trap-Andersen S. The influence of alfentanil on the intubating conditions after priming with vecuronium. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 41–44.
8. Steyn M, Quinn A, Gillespie J, Miller D, Best C, Morton N. Tracheal intubation without neuromuscular block in children. *British Journal of Anaesthesia* 1994; **72**. 403–406.
9. Westmoreland C, Hoke J, Sebel P. Pharmacokinetics of remifentanil (G187084B) and its major metabolite (GR90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 1993; **79**. 893–903.
10 Kharash E, Russell M, Mantz D, Thummel K, Kunze K, Bowdle T, Cox K. The role of cytochrome P450 3a4 in alfentanil clearance: implications for interindividual variability in disposition and perioperative drug interactions. *Anesthesiology* 1997; **87**: 36–50.
11. Kapilla A, Glass P, Jacobs J. Measured context-sensitive half-times of remifentanil and alfentanil. *Anesthesiology* 1995, **83**: 968–975

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LABORATORY INVESTIGATIONS

Performance of proportional and continuous nitric oxide delivery systems during pressure- and volume-controlled ventilation†

M. J. Hiesmayr, T. Neugebauer, A. Laßnigg, H. Steltzer, W. Haider and H. Gilly

Summary

We have evaluated the effect of delivering nitric oxide using a continuous flow system (CFS) or two commercially available proportional gas injection systems (PGIS), Nodomo (Dräger, Lübeck, Germany) and Pulmonox-Mini (Messer Griesheim Austria, Gumpoldskirchen, Austria) on measured and simulated concentrations of nitric oxide. Nitric oxide concentration was measured in a bench test at five sites in the inspiratory breathing system during volume- or pressure-controlled ventilation and mathematically simulated using a mixing chamber model. For a target concentration of 10 parts per million (ppm) at the "Y" piece, simulated nitric oxide concentrations were 1.9–139 ppm for CFS, 0.3–22 ppm for the Nodomo and 0.0–31 ppm for the Pulmonox-Mini near the nitric oxide administration site. However, peak concentrations decreased rapidly along the inspiratory system. Measured and simulated variations depended on the nitric oxide delivery system, site of measurement and tidal volume. Measured variations were four times smaller in the Nodomo than in the Pulmonox-Mini and CFS. As inappropriate mixing may occur even with PGIS, nitric oxide should probably not be administered near the "Y" piece. (*Br. J. Anaesth.* 1998; **81**: 544–552).

Keywords: pharmacology, nitric oxide; equipment, breathing systems

Inhalation of nitric oxide at low doses[1] has been used for the treatment of ARDS,[2] persistent fetal circulation of the newborn[3] and right heart failure.[4] Ideally, nitric oxide administration techniques should generate precise and homogeneous mixtures of NO with the inspired gas.[5] Techniques for adding small amounts of nitric oxide to the inspired gas may be categorized into continuous flow systems (CFS) that inject nitric oxide–nitrogen throughout the respiratory cycle,[5–8] proportional gas injection systems (PGIS) that inject nitric oxide–nitrogen in proportion to the inspiratory gas flow[2 9–11] and non-proportional gas injection systems[12] during inspiration. In theory, only PGIS should consistently generate precise and homogeneous nitric oxide mixtures, while CFS are known to generate inhomogeneous nitric oxide mixtures.[6 13–16] Non-proportional gas injection systems triggered by airway pressure appear to deliver relatively homogeneous mixtures during ventilation.[12] The performance of two commercial PGIS has been assessed recently.[11 17] However, no direct comparison was made with the widely used CFS using the same measurement set-up. A single measurement set-up appears to be necessary because of the widely variable results obtained, even with fast-response measurements.[12 14]

The aim of this study was to assess the homogeneity and precision of gas mixing, on the basis of measured maximal, minimal and mean nitric oxide concentrations in a bench test, and by mathematical simulation of "true" nitric oxide concentrations (NO_{sim}) using a mixing chamber model. The precision of gas mixing was analysed by comparing measured concentrations of nitric oxide (NO_{meas}) with set concentrations for the PGIS, and calculated concentrations for CFS[18] during pressure- and volume-controlled ventilation of a test lung. Measurements were obtained at five sites along the inspiratory limb to reveal inhomogeneities related to nitric oxide delivery systems and to estimate the effect of shortening the distance between the site of injection of nitric oxide and the site where the nitric oxide mixture enters the lung.

Materials and methods

EXPERIMENTAL SET-UP

For all experiments a commercial test lung (LF 800, Drägerwerk, Lübeck, Germany) was ventilated with a ventilator (Evital, Dräger, Lübeck, Germany) in either volume- or pressure-controlled mode. As this lung model is designed only for controlled ventilation, spontaneous breathing patterns could not be studied. Ventilatory frequencies were 10, 20 and 30 bpm. We investigated small (300–400 ml), moderate (600–700 ml) and large (900–1000 ml) tidal volumes. The ratio of inspiratory to expiratory time was maintained constant (1:2). The inspiratory flow rate was the same at each tidal volume. During volume-controlled ventilation, inspiratory flow was set to 0.5 litre s^{-1} for a ventilatory frequency of 10 bpm, 1 litre s^{-1} for 20 bpm and 1.5 litre s^{-1} for 30 bpm. During pressure-

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†Preliminary data have been presented at the Annual Meeting of the American Thoracic Society, New Orleans, 1996.

controlled ventilation, we adjusted inspiratory pressure to achieve the same tidal volumes as those during volume-controlled ventilation. During pressure-controlled ventilation, two series of measurements were performed: the first series using the same compliance of 35 ml cm H_2O^{-1} of the total respiratory system as during volume-controlled ventilation and the second series after having reduced compliance by approximately 50%.

The standard respiratory breathing system consisted of disposable corrugated plastic tubing with a diameter of 22 mm (Laborex, Vienna, Austria) and a humidifier (MZ 290 Fisher Paykel, NZ Techno, Auckland, NZ) with a residual gas volume of 300 ml when filled. At six sites in this inspiratory limb, a connector designed for injecting or sampling gas in mid-stream (Gas line adapter 15M/15F&22M, Vital Signs, NJ, USA) was inserted. The nitric oxide injection site was 20 cm downstream from the inspiratory outlet of the ventilator. Five measurement sites were chosen: site A=20 cm after the nitric oxide injection site, site B=60 cm after the nitric oxide injection site, site C=immediately after the humidifier, site D=100 cm and site E=20 cm before the "Y" piece (fig. 1). The length between the nitric oxide injection site and the sampling site near the "Y" piece was 220 cm and volume 1136 ml. The nitric oxide mixture was sampled via lines of equal length (Gas sampling interface 5640CEI, Vital Signs, NJ, USA).

MEASUREMENT EQUIPMENT

Nitric oxide concentration was measured using a chemiluminescence analyser (MLU 8840, Monitor Laboratories; 90% step response 3 s and a transport delay of 980 ms because of the sampling line; MLU Mödling, Austria). The nitric oxide mixture was sampled at a flow of 500 ml min^{-1}. The device was calibrated before each set of measurements using certified gas mixtures containing nitric oxide–nitrogen 10±1 ppm (AGA, Schwechat, Austria). Inspiratory flow and tidal volume were measured with an ultrasonic flowmeter (Spiroson, Isler Bioengineering, Dürnten, Switzerland) after site E. Nitric oxide concentration, flow and volume data were digitized at 200 Hz and stored in a PC (Breath for MS Windows, Isler Bioengineering, Dürnten, Switzerland).

To provide estimates of the mixing variables for the mathematical simulation, measurements with 26% carbon dioxide–nitrogen (AGA, Schwechat, Austria) were performed. Carbon dioxide concentrations were measured with a fast-response sidestream infrared analyser (90% step response time 300 ms, transport delay 1050 ms; Datex Oscar Oxy, Datex, Turku, Finland) calibrated according to the manufacturer's instructions.

NITRIC OXIDE DELIVERY SYSTEMS

Nitric oxide was injected into the inspiratory limb always at the same point. In all experiments the target nitric oxide concentration (NO_{target}) was 10 ppm.

The Nodomo (Dräger, Lübeck, Germany) was linked to an Evita1 ventilator (Dräger, Lübeck, Germany) according to the manufacturer's recommendations. The Nodomo receives the flow signal directly from the ventilator and injects the nitric oxide–nitrogen mixture (1000 ppm) in proportion to inspiratory flow.

The Pulmonox-Mini (Messer-Griesheim, Gumpoldskirchen, Austria) uses an external flowmeter that can be inserted into any respiratory system to measure inspiratory flow. This external flowmeter is specified for a maximal inspiratory flow of 1 litre s^{-1}. The Pulmonox-Mini injects the nitric oxide–nitrogen mixture (950 ppm) in proportion to measured inspiratory flow using a mass flow controller. According to the manufacturer's instructions, the nitric oxide–nitrogen mixture should be injected near the "Y" piece and measured close to this site. To facilitate comparison with other systems, in our set-up, the nitric oxide–nitrogen mixture was injected 20 cm downstream of the ventilator (fig. 1).

For the CFS, an electronic flowmeter (DelNO 1000, Sensormedics, Yorba Linda, CA, USA) was

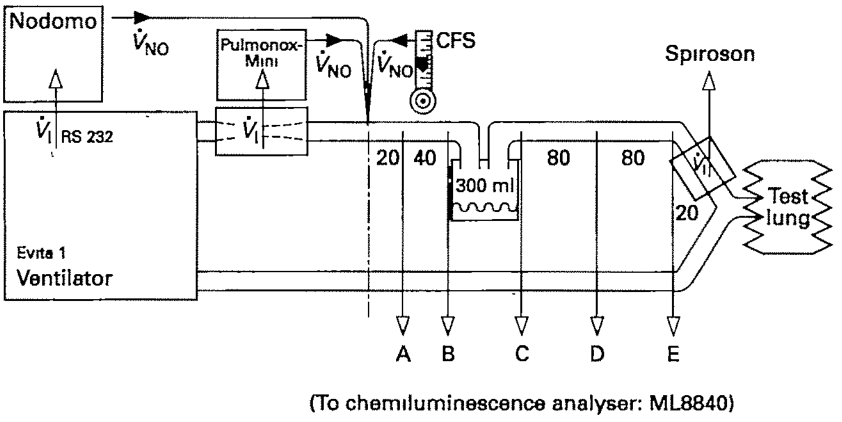

Figure 1 Diagrammatic representation of the experimental set-up. Nitric oxide in nitrogen (NO/N_2) was injected into the inspiratory system of a standard disposable respiratory breathing system of corrugated plastic tubing with an internal diameter of 22 mm by a continuous flow system (CFS) or by two proportional gas adding systems (PGIS). The Nodomo injects NO/N_2 in proportion to the inspiratory flow signal ($\dot{V}_{I\,RS232}$) provided by the ventilator, and the Pulmonox-Mini injects NO/N_2 in proportion to inspiratory flow ($\dot{V}_{I\,meas}$) measured by an orifice type flowmeter. With CFS, the NO/N_2 mixture flow is calculated and set by the operator. The distance between the five sampling sites, A–E, is given in centimetres. The length between site A and site E near the "Y" piece was 200 cm. The humidifier had a residual volume of 300 ml. $\dot{V}_I$ is inspiratory flow from the ventilator and $\dot{V}_{NO}$ is NO/N_2 gas flow (closed arrows). Sampling of inspired gas for measurement of nitric oxide concentration is indicated by the open arrows.

used to provide a constant nitric oxide–nitrogen (1000 ppm) flow ($\dot{V}_{NO}$) into the inspiratory system. $\dot{V}_{NO}$ was calculated according to equation (1) given by Young and Dyar,[18] to yield a mean fractional inspired (target) concentration (FI_{NO}) of nitric oxide of 10 ppm in the inspired gas.

$$\dot{V}_{NO}=\dot{V}_I\,(FI_{NO}/(F_{NO/N2}-FI_{NO})) \qquad (1)$$

where $\dot{V}_{NO}$=flow of nitric oxide–nitrogen mixture, $\dot{V}_I$ =inspired minute ventilation, $F_{NO/N2}$= fractional concentration of nitric oxide in the nitric oxide–nitrogen mixture, and FI_{NO}= fractional inspired (target) concentration of nitric oxide.

Thus in our set-up, where the nitric oxide concentration in the nitric oxide–nitrogen mixture was 1000 ppm, $\dot{V}_{NO}$ was set to 1% $\dot{V}_I$.

NUMERICAL SIMULATION

We developed a numerical simulation to estimate the true maximal and minimal nitric oxide concentrations. This simulation uses a radial mixing chamber model and standard formulae[19] to describe gas flow in the inspiratory system.

Gas flow model

The cross-sectional profile of gas flow in a tube is dependent on the Reynolds number (*Re*):

$$Re=\bar{v}\times d/\nu \qquad (2)$$

where $\bar{v}$=spatial mean velocity, d=diameter and ν=kinematic viscosity, which is 15.58 10^{-6} m^2 s^{-1} at 25°C for air. When $Re > Re_{crit}$, the flow profile changes from laminar to turbulent. Re_{crit} in a tube is approximately 2320. At the outlet of the ventilator and near connectors, turbulent flow may exist even at $Re < Re_{crit}$, but flow reverts back to laminar if undisturbed.

The laminar profile is parabolic. The ratio of the velocity $v(r)$ at the radius r to the velocity *v*max in the centre of a tube with diameter *d* is:

$$v(r)/v_{max}=((d/2)^2-r^2)/(d/2)^2=(1-r^2/(d/2)^2) \qquad (3)$$

and by integration:

$$v_{max}=2\bar{v} \qquad (3a)$$

The turbulent profile is flatter and described by:

$$v(r)/v_{max}=((d/2-r)/(d/2))^{1/n}=(1-r/(d/2))^{1/n} \qquad (4)$$

and by integration:

$$v_{max}=\bar{v}(n+1)(2n+1)/2n^2 \qquad (4a)$$

where n depends on *Re* and varies between 5.4 and 6.4 for flows of 0.5–2.0 litre s^{-1}. In this simulation, n was set to 6.

The ratio of instantaneous inspiratory flow velocity generated by the ventilator ($\bar{v}$) and *v*max is therefore 1.26 for turbulent flow and 2.0 for laminar flow. Even when flow is turbulent, a peripheral zone of laminar flow persists. The thickness of this zone is termed ∂_1,

$$\partial_1=34.2d(0.5\,Re)^{0.875} \qquad (5)^{19}$$

with a parabolic velocity distribution according to equation (3). At a flow of 0.57 litre s^{-1} when $Re=Re_{crit}$, ∂_1=7.1% of the diameter and thus the cross-sectional volume of laminar flow is 26.4%. At the maximal flow of 2.0 litre s^{-1} generated by the ventilator, this volume decreases to 9.4%.

At the border of the turbulent and laminar zone, laminar flow velocity and turbulent flow velocity were set to be equal. Therefore, equation (3) becomes:

$$v(r)=(1-r^2/(d/2)^2)\times(1-\partial_1/(d/2))^{1/n}/(1-\partial_1^2/(d/2)^2)\times v_{max} \qquad (6)$$

for the laminar zone, with *v*max derived from turbulent flow velocity.

Determination of local nitric oxide concentrations

For the numerical simulation, both central turbulent and peripheral laminar flow profiles were used because at inspiratory flows used in clinical practice, the relevant *Re* is close to Re_{crit}. The inside of the tube was divided into volume elements. The cross-sectional flow profile, as described above, was used to determine the axial movement of these volume elements. The nitric oxide concentration at the distance x, downstream from the site where nitric oxide–nitrogen is injected to the inspired gas, was obtained by averaging the concentration data of all volume elements at x.

The inspiratory limb was assumed to be a rigid annular tube with a constant diameter (d) and length (l). The tube was divided into N_x elements (index I) of length $\Delta x=l/N_x$ and a volume of $\Delta V=(d/2)^2\times\pi\times\Delta x$. One such cylinder element was subdivided into N_r concentric tubular elements (index j) with the outer radius r_j and inner radius r_{j-1} The radius of each element was chosen to yield identical volumes ΔV_{ij} for each element within one flow zone.

$$\Delta V_{ij}=(r_j^2-r_{j-1}^2)\times\pi\times\Delta x \qquad (7)$$

The total gas volume contained in the inspiratory system thus consisted of N_xN_r volume elements. Each element moves during the time interval Δt according to the axial velocity $v_j(r,t)$ given by equations (3) and (4) over a distance $\Delta x_j(r,t)=v_j(r,t)\times\Delta t$. The time interval Δt was selected in such a way that the central element moves over the length Δx within Δt.

The nitric oxide concentration $c_{ij}(x,r,t)$ within each element was calculated at each step. At each step nitric oxide was exchanged between contiguous elements. As contiguous elements are aligned only at the start of simulation, the exchange of nitric oxide was weighted in proportion to the overlapping area of contiguous elements. The fraction exchanged was determined empirically by fitting fast-response data obtained with carbon dioxide as a tracer gas to simulated data. In all simulations we used a 10% longitudinal mixing fraction and a 3–12% lateral mixing fraction, depending on Δt. The humidifier was assumed to be a similar tube with the maximal mixing fraction allowed by the model (30% longitudinal, 25% lateral). The mixing fraction was identical for all experimental conditions. Concentrations were averaged for any distance x from the nitric oxide injection site:

$$c_i(x,t)=\sum_{j=1}^{N_r}c_{ij}(x,r,t)\Delta V_{ij}/\Delta V \qquad (8)$$

These simulated concentrations (NO_{sim}) were considered to be an estimate of true nitric oxide concentrations (NO_{true}). They were calculated with a resolution Δx of 2 cm for any moment within the respiratory cycle. In our experimental set-up, gas for sidestream measurement of nitric oxide concentration was sampled in the middle of the inspiratory gas stream. Thus NO_{meas} should represent the concentration of nitric oxide in the major part of a tidal volume, but should be slightly more variable than NO_{sim}, which is an average over the whole cross-section. We did not assess the effect of sampling from different points in the cross-section of the tube.

To be able to compare NO_{sim} with NO_{meas}, low-pass filtering of NO_{sim} was necessary to account for the 90% response time (t_{90}) of 100–3000 ms of the different nitric oxide analysers. Low-pass filtered nitric oxide concentration (NO_{filter}) was calculated at the time point t as:

$$NO_{filter(t)} = a \times NO_{filter(t-\Delta t)} + (1-a) \times NO_{sim(t)} \qquad (9)$$[20]

where $a = e^{-\Delta t/\tau}$ and the time constant $\tau = -t_{90}/\ln(0.1)$.

Two respiratory flow patterns were implemented. One pattern corresponded to conventional volume-controlled ventilation with a constant inspiratory flow and was used to evaluate the CFS. The second pattern simulated pressure-controlled ventilation with a typical decelerating flow. The deceleration profile was set to be linear for two reasons: first for simplicity and second because measured inspiratory flow from the ventilator did not show an exponential fall during pressure-controlled ventilation. In addition, the model for decelerating flow allowed the introduction of a delay between the beginning of the inspiratory flow from the ventilator and the beginning of injecting nitric oxide–nitrogen by the PGIS. If the flow is decelerating, such a delay causes the instantaneous $\dot{V}_{NO}$ to be too large for the actual inspiratory flow, and thus the nitric oxide concentration in the inspired gas is above the desired concentration.

The simulation was developed in Turbo C+ (Borland) and executed in a DOS window of MS Windows NT 3.51.

DATA PRESENTATION AND STATISTICAL ANALYSIS

The maximal (NO_{max}), minimal (NO_{min}) and mean (NO_{mean}) nitric oxide concentrations were determined during each of three consecutive respiratory cycles and averaged for the three cycles. These average values were used for statistical analysis. Data were compared using two-way ANOVA with repeated measurements to determine differences in NO_{meas} and deviations from NO_{target} between the five sites of measurement within each delivery system and between delivery systems. The independent variables were the delivery systems and tidal volume, and the five sites were the repeated measures; all effects were considered to be fixed. To assess the combined effect of sampling site, tidal volume and ventilatory frequency, multiple regression, including interaction between site, tidal volume and type of ventilation, was calculated. *Post-hoc* analysis was performed with Tukey's method for multiple comparisons. All statistical analyses were performed using Systat for Windows (version 5.01, 1992, Evanston, IL, USA). $P<0.05$ was considered significant. Data are presented as mean (range). SD values were determined only to evaluate the overall variability of the differences between NO_{target}, and NO_{max}, NO_{mean} and NO_{min}, respectively, for all sampling points at once.

Results

Nitric oxide concentrations, measured (NO_{meas}) by chemiluminescence with a response time of 3 s, varied between 1 and 23 ppm when NO_{target} was 10 ppm (fig. 2). NO_{meas} depended on the nitric oxide delivery system ($P<0.0001$), site of measurement ($P<0.0001$) and tidal volume ($P<0.0001$), but was independent of ventilatory frequency.

EFFECT OF THE NITRIC OXIDE DELIVERY SYSTEM

Deviations from NO_{target} along the inspiratory limb were small for the Nodomo with an SD of 1.0 but larger for the Pulmonox-Mini (3.6) and CFS (4.2). The difference between measured NO_{max} and NO_{min} at any one site was less ($P<0.001$) with the Nodomo (range 0.2–1.76 ppm) than for both the Pulmonox-Mini (0–7.0 ppm) and CFS (0.2–5.4 ppm). Only with the Pulmonox-Mini did the measured difference between NO_{max} and NO_{min} decrease along the inspiratory limb. At site E, nearest to the "Y" piece, NO_{meas} was mean 9.6 (range 8.8–10.6) ppm for the Nodomo, 9.3 (6.8–12.6) ppm for the Pulmonox-Mini and 11 (5–23) ppm for the CFS.

EFFECT OF SITE AND TIDAL VOLUME

With the Pulmonox-Mini and CFS, large peaks and troughs in nitric oxide concentrations were found at specific sites along the inspiratory limb. At site A, near the injection site of nitric oxide into the inspiratory system, NO_{meas} was always less than NO_{target} for the CFS, whereas for both the Nodomo and Pulmonox-Mini, NO_{meas} was mostly greater than NO_{target}, especially during pressure-controlled ventilation. At site A, the deviation above NO_{target} was twice as large for the Pulmonox-Mini than for the Nodomo. At site E, NO_{meas} was consistently less than NO_{target} during pressure-controlled ventilation only for the Pulmonox-Mini.

SIMULATED "TRUE" NITRIC OXIDE CONCENTRATIONS

NO_{sim} varied considerably near the site where nitric oxide was injected into the inspiratory system, and much less towards the end of the inspiratory system when dilution and mixing had occurred (fig. 3). For CFS, a bolus of nitric oxide–nitrogen at high concentration accumulated near the injection site during expiration and this bolus was diluted along the inspiratory limb (fig. 3). The size of the bolus depends on the flow of nitric oxide–nitrogen set on the continuous flowmeter and length of time where there is no inspiratory flow (e.g. inspiratory pause + duration of expiration). We calculated the required nitric oxide–nitrogen flow according to equation (1)[18]; the size of the bolus decreased with smaller tidal volumes. When smaller tidal volumes were used, the smaller bolus size reduced the difference between NO_{true} and NO_{target}, thus improving mixing along the inspiratory limb (fig. 4). For PGIS, we assessed the effect of a delay between the beginning of inspiration and the beginning of injection of nitric oxide–nitrogen, in addition to the effect of a similar delay between the end of inspiration and end of injection of nitric oxide–nitrogen. With such a delay, there is no injection of nitric oxide–nitrogen during the beginning of

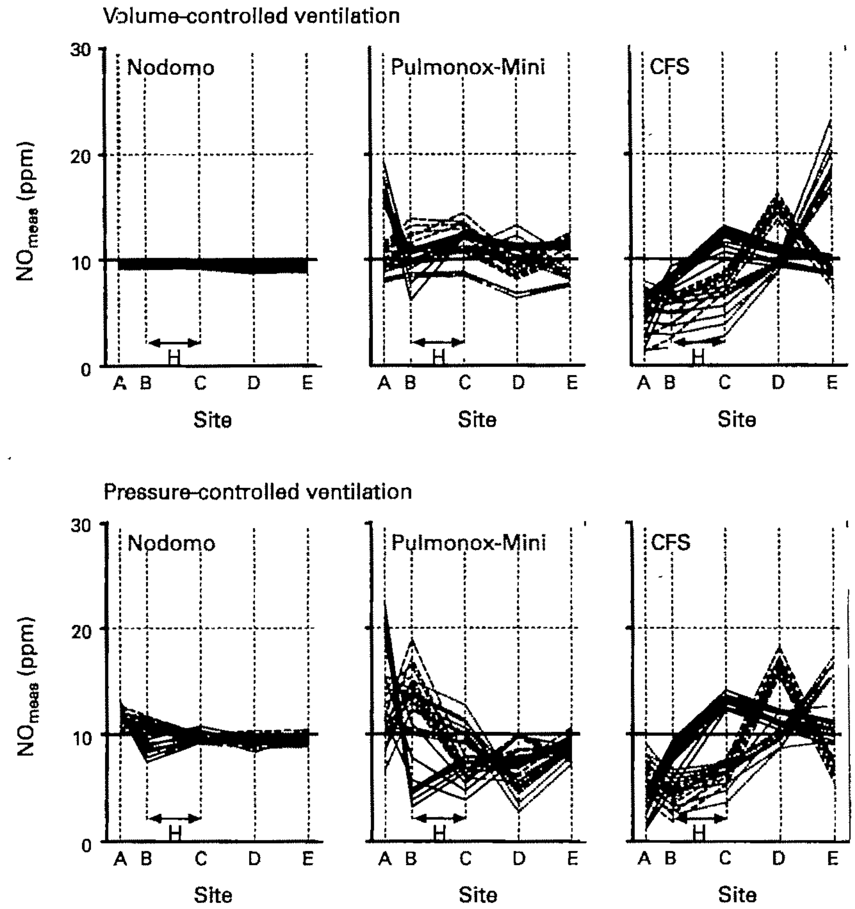

Figure 2 Nitric oxide concentration (NO$_{meas}$) measured by chemiluminescence during volume-controlled and pressure-controlled ventilation of a test lung. Nitric oxide in nitrogen (NO/N$_2$ mixture) was added 20 cm before site A into the inspiratory limb of a standard disposable respiratory system via two proportional gas adding systems (Nodomo and Pulmonox-Mini) or via a continuous flow system (CFS). Tidal volume was 300–400 ml (solid lines), 600–700 ml (broken lines) and 900–1000 ml (dotted lines); ventilatory frequency was 10, 20 or 30 bpm. The resulting maximal, minimal and mean nitric oxide concentrations over a respiratory cycle (and averaged over three cycles) are each represented by an individual line for each ventilatory frequency. H=Humidifier.

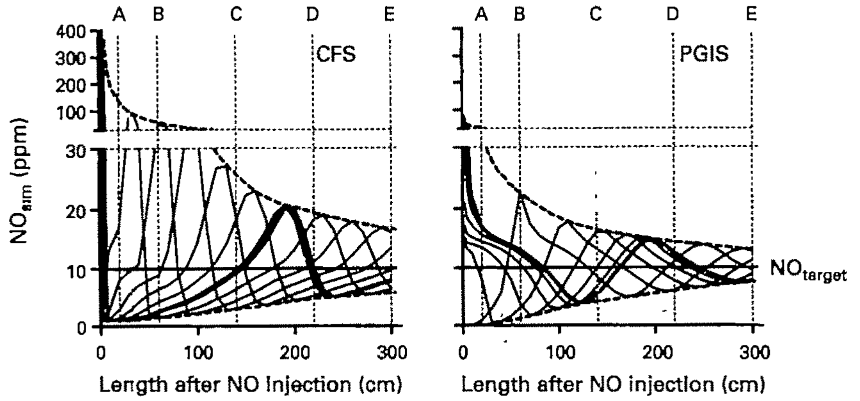

Figure 3 Simulation of "true" nitric oxide concentrations (NO$_{sim}$) during transport and dilution of nitric oxide in nitrogen (NO/N$_2$ mixture) along the inspiratory system. The NO$_{sim}$ profile is shown at intervals of 100 ms during two consecutive breaths, with a tidal volume of 600 ml for CFS during volume-controlled (left) ventilation and for PGIS during pressure-controlled ventilation (right) at a ventilatory frequency of 10 bpm. The majority of these curves represent the concentration profiles during expiration where inspiratory gas moves only very little, leading to the thick curve which peaks at 0 and 200 cm. Maximal and minimal NO$_{sim}$ is indicated by a broken line. The PGIS was assumed to inject NO/N$_2$ with a delay of 100 ms in relation to the inspiratory flow from the ventilator. The solid horizontal line indicates the target nitric oxide concentration (NO$_{target}$) of 10 ppm. A–E indicate sampling sites, as used in figures 1 and 2.

inspiration, and a small bolus of nitric oxide–nitrogen accumulates immediately after the end of inspiration. We assessed delays of 50, 100 and 150 ms, because such delays are characteristic for the opening of a valve or starting a mass-flow controller. The effects were smaller during volume-controlled ventilation (data not shown) than during pressure-controlled ventilation (fig. 5). At a delay of 150 ms, the deviations from NO$_{target}$ were still as large as +80 and −70% after 100 cm of mixing along the inspiratory system.

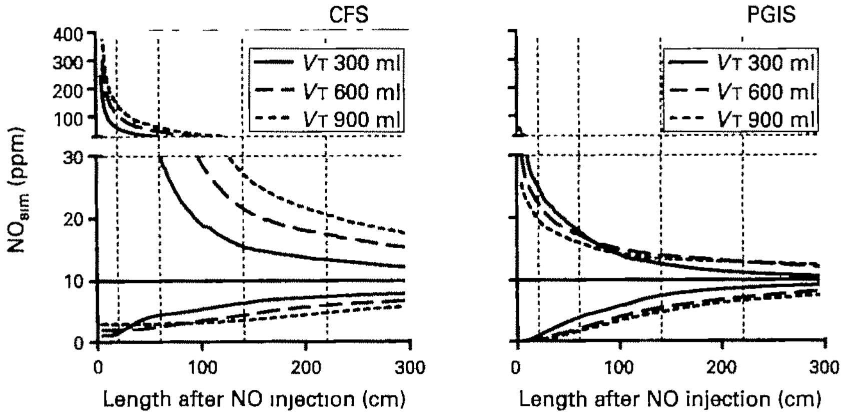

Figure 4 Simulated "true" nitric oxide concentrations (NO_{sim}) along the inspiratory system depended on tidal volume (*V*T) for CFS during volume-controlled ventilation or for PGIS during pressure-controlled ventilation. Ventilatory frequency was set at 10 bpm. The PGIS was assumed to inject nitric oxide in nitrogen (NO/N_2 mixture) with a delay of 100 ms in relation to inspiratory flow from the ventilator. The solid horizontal line indicates NO_{target} and the vertical dotted lines the measurement sites A–E.

Near the "Y" piece, the deviations were approximately 50% smaller than those found for CFS. In contrast with the CFS, the inhomogeneity with PGIS near the site where nitric oxide was injected into the inspiratory system was larger at smaller tidal volumes (fig. 4).

EFFECT OF RESPONSE TIME OF THE NITRIC OXIDE ANALYSER

We applied low-pass filtering to NO_{sim} to investigate to what extent the inhomogeneities generated by the nitric oxide delivery systems were traceable. We used a response time of 100 ms to compare with the best available technology,[14] a response time of 300 ms to compare with measurements performed with carbon dioxide instead of nitric oxide, and a response time of 3000 ms to compare with standard equipment, as used recently[12] and in this study. We did not investigate the performance of the most widely used electrochemical cells with response times of 5–15 s.

Our results suggested that precise measurements can be obtained with a response time of 100 ms but that the peak nitric oxide concentration was underestimated in our test set-up by as much as 100 ppm within the first 30–50 cm after injection of nitric oxide–nitrogen when CFS were used (fig. 6). With a response time of 300 ms, peak concentrations were underestimated along the whole length of the respiratory system and with a response time of 3000 ms, NO_{sim} was measured only at specific sites in the inspiratory limb. These sites depended on tidal volume. In addition, the sites where peak NO_{sim} was measured were distinct from those where trough NO_{sim} was measured. Thus measurements at a single site revealed any value between peak NO_{sim} and trough NO_{sim}, depending on position and tidal volume. The same was true for PGIS. During pressure-controlled ventilation and a response time of 3000 ms, NO_{meas} was always greater than NO_{target} near the site where nitric oxide–nitrogen was injected by the PGIS. The magnitude of this deviation above NO_{target} was proportional to the delay time of the nitric oxide delivery device (data not shown).

Discussion

We have investigated both time-dependent and spatial nitric oxide mixing along the inspiratory limb for PGIS and CFS, by simultaneous measurements at multiple sites and by mathematical simulation of the transport and mixing processes. We have shown clearly that inhomogeneous mixing of nitric oxide with the inspiratory gas is not unique to the most widely used CFS[8] that inject a continuous flow of nitric oxide–nitrogen throughout the respiratory cycle, but is also, to a lesser extent, typical for some PGIS designed to inject nitric oxide–nitrogen in proportion to inspiratory flow.[9] Inhomogeneous mixing of nitric oxide always occurs during mechanical ventilation when nitric oxide–nitrogen is not injected simultaneously and in exact proportion to inspiratory flow.

For CFS, inhomogeneous nitric oxide mixtures are unavoidable as nitric oxide–nitrogen at a high concentration (e.g. 300–1000 ppm) accumulates during expiration at the injection site, creating a bolus which is transported and diluted along the respiratory system during inspiration. Therefore, it is not surprising that for CFS, very high peak NO_{meas} exceeding NO_{target} by factors of 2.4,[16] 3.0[6] and 5.0[5 13] have been reported. This large variability between observed peak NO_{meas} may be explained by different measurement technologies, such as fast- *vs* slow-response chemiluminescence[14 16] or by the use of a tracer gas such as nitrogen[6] or carbon dioxide[5 13] (instead of nitric oxide) which provide the advantage of rapid analysis. The highest peak NO_{meas} exceeded NO_{target} by a factor of 12.5 for CFS,[14] but these investigators added 2–4 times more nitric oxide–nitrogen for a given minute ventilation than all other investigators who used equation (1).[18] Thus the very high peak NO_{meas} reported by Imanaka and colleagues[14] was caused not only by a fast-response chemiluminescence device but also by a higher dose of nitric oxide. In fact, nitric oxide–nitrogen flow was identical, regardless of whether nitric oxide–nitrogen was injected during inspiration only or throughout the respiratory cycle. In addition, the highest peak NO_{meas} did not occur near the injection site but 90 cm down-

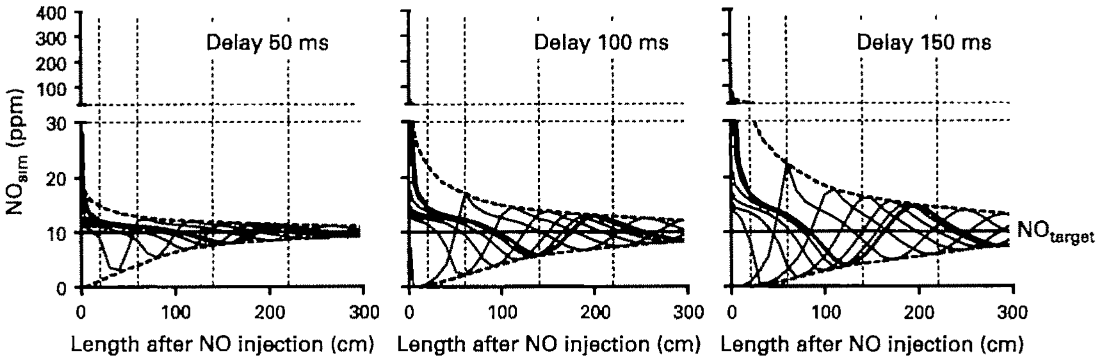

Figure 5 Deviations of NO$_{sim}$ from NO$_{target}$ in relation to the delay between nitric oxide in nitrogen (NO/N$_2$ mixture) injection and inspiratory flow from the ventilator in the PGIS The NO$_{sim}$ profile is shown at intervals of 100 ms during pressure-controlled ventilation with a tidal volume of 600 ml and a ventilatory frequency at 10 bpm. Maximal inspiratory flow was set to 2 litre s^{-1}. The solid horizontal line indicates NO$_{target}$ and the vertical dotted lines the measurement sites A–E.

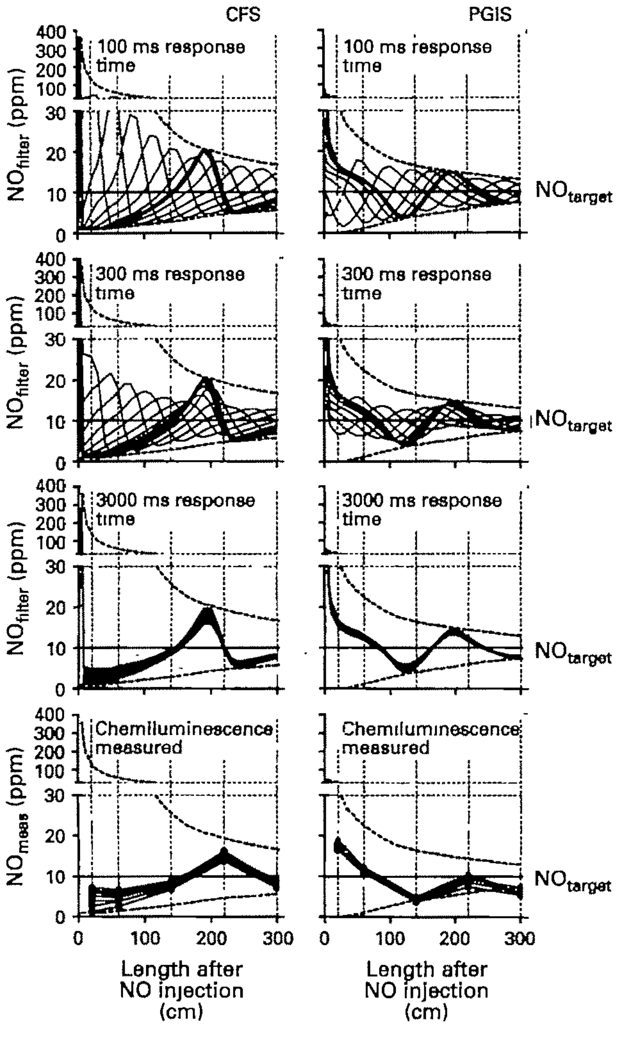

Figure 6 Simulated effect of response time of nitric oxide measuring equipment on the measured nitric oxide concentrations along the inspiratory system. A response time for a 90% step response of 100, 300 and 3000 ms was simulated by low-pass filtering NO$_{sim}$ of data obtained by simulation (see fig. 3) of CFS (left) during volume-controlled ventilation and of PGIS (right) during pressure-controlled ventilation with a tidal volume of 600 ml and a ventilatory frequency of 10 bpm. The PGIS was assumed to inject nitric oxide in nitrogen (NO/N$_2$ mixture) with a delay of 100 ms in relation to inspiratory flow from the ventilator. The NO$_{filter}$ profile is shown at intervals of 100 ms by solid lines, maximal and minimal NO$_{sim}$ by dashed lines, target nitric oxide concentration (NO$_{target}$) by a horizontal solid line and the position of the measurement sites A–E by vertical dotted lines. The bottom panel shows NO$_{meas}$ obtained by chemiluminescence in the test set-up with a response time of 3000 ms (closed circles) for CFS and the Pulmonox-Mini.

stream. This finding is in agreement with our simulation, where we demonstrated that within the first 30–50 cm after the site of injecting nitric oxide–nitrogen, fast-response chemiluminescence may underestimate the true peak concentration by as much as 100 ppm when NO$_{target}$ is set to 10 ppm and nitric oxide concentration in the nitric oxide–nitrogen mixture is 1000 ppm. Although the inhomogeneity of the nitric oxide mixture for CFS is considerable, especially near the injection site, we found that peak NO$_{sim}$ decreased rapidly along the inspiratory limb (fig. 4) and that the inhomogeneity may be reduced further by using small tidal volumes (fig.5). Thus nitric oxide–nitrogen should be injected near the ventilator to allow better mixing along the inspiratory circuit and to prevent highly inhomogeneous nitric oxide mixtures from entering the lung. What was beyond the scope of this investigation was how mixing progresses within the airways, but we believe that if nitric oxide is not reasonably mixed before entering the lung, areas with very different compliance may be exposed to different nitric oxide concentrations. Low concentrations in the alveoli and high concentrations in the airways also appear possible. Further investigations that relate clinical effects to the adequacy of mixing are necessary.

CFS are still widely used[8] and are provided as backup systems for all types of PGIS. Because rotameters are independent of power sources, they are also used when transporting critically ill hypoxic patients. Our simulation demonstrated that NO$_{true}$ varies by less than ±25% from NO$_{target}$ at the "Y" piece when sufficient mixing is allowed and small tidal volumes are used.

PGIS are considered to provide an optimal solution for administration of nitric oxide.[9] The performance of two such delivery systems[11 17] has been assessed recently in bench tests. In our study, direct comparison of two PGIS showed that they differed considerably in performance and that they may also generate highly inhomogeneous nitric oxide mixtures. For the Nodomo, where the ventilator provides accurate instantaneous inspiratory flow data, the overall performance was good, whereas for the Pulmonox-Mini, where inspiratory flow was measured independently, overall performance was much more variable. For the Pulmonox-Mini, we found that NO$_{meas}$ deviated four times more from NO$_{target}$ than the Nodomo along the inspiratory limb. In addition, during volume controlled ventilation, NO_{meas} near the "Y" piece at the smaller tidal volumes was 20–30% greater than NO_{target} at an inspiratory flow of 1 litre s^{-1} and decreased by 35% from this maximal value when inspiratory flow was doubled. Moreover, NO_{meas} also decreased slightly when inspiratory flow was halved (data not shown). We believe that incorrect dosing of the Pulmonox-Mini is caused by an insufficient dynamic response in the measurement of inspiratory flow rather than to an upper limit in the amount of injected nitric oxide–nitrogen, because incorrect dosing was associated with a high inspiratory flow but not clearly with a large tidal volume. This flow dependence may be caused by non-linearity of flow measurement as the flow range specified for the Pulmonox-Mini is less than 1 litre s^{-1}.

During pressure-controlled ventilation with the typical decelerating inspiratory gas flow, both PGIS generated a distinct concentration profile along the inspiratory system. Nitric oxide concentrations were nearly always greater than NO_{target} at site A, near the injection site (fig. 2). At all other sites moderate peaks and troughs in nitric oxide concentrations were recorded, depending on tidal volume (fig.2) and the compliance of the test lung (data not shown). As this observation was highly reproducible in PGIS, it may be concluded that a systematic phenomenon generating inhomogeneous nitric oxide mixtures exists.

Theoretically, homogeneous nitric oxide mixtures should be generated with PGIS not only near the injection site but also downstream. We always found higher NO_{meas} near the injection site. The amount of injected nitric oxide–nitrogen is too large if the end of the inspiratory flow is not sensed correctly by the flowmeter or if nitric oxide–nitrogen is injected with a delay in relation to inspiratory flow. When we used a delay of 50–150 ms in our simulation with the mixing chamber model, we found a nitric oxide concentration profile along the inspiratory limb that matched the measured profile for both PGIS. A delivery delay of approximately 100 ms is plausible based on the time required to control the nitric oxide–nitrogen delivery system which uses a valve assembly. If such a delay exists, it results in overdosing at the end of inspiration and underdosing during the first 100 ms of inspiration because no nitric oxide–nitrogen is injected at this time. With pressure-controlled ventilation, inspiratory flow increases up to 2 litre s^{-1} in less than 100 ms; during this time an inspiratory volume of 130 ml is provided. Thus, up to one-third of a small tidal volume may not contain any nitric oxide. In fact, NO_{meas} was as low as 2.8 ppm for the Pulmonox-Mini and 7.5 ppm for the Nodomo. We estimated NO_{true} to be as low as 0.2 ppm at a delivery delay of 100 ms by simulation. Thus during pressure-controlled ventilation, PGIS generate inhomogeneous nitric oxide mixtures with peak concentrations that are much lower than those in CFS, but troughs that are more profound than those generated by CFS. In the Pulmonox-Mini, which works with all types of ventilators because inspiratory flow is measured independently, we found larger inhomogeneities than in the Nodomo where the linked ventilator provides a flow signal simultaneously with inspiration. We suggest that to improve mixing in PGIS, nitric oxide–nitrogen should be injected near the ventilator to allow mixing in the inspiratory limb, especially for the Pulmonox-Mini.

Monitoring of nitric oxide concentrations, to ensure correct dosage, is only reliable when homogeneous mixing is ensured at the site of measurement. We found NO_{meas} to be greater or less than NO_{target} along the inspiratory system (fig. 2). When a large tidal volume was used in the CFS, NO_{meas} increased progressively from the injection site towards the "Y" piece. Apparently, similar findings by other authors created the impression that nitric oxide concentrations generated by such systems are unpredictable.[13 14 16 21] However, in this context the effect of slow-response nitric oxide analysers, which are used mainly in the clinical setting, should be outlined. In fact, slow-response nitric oxide analysers measure mainly a time-averaged concentration, whereas a volume-averaged concentration would be of greater interest clinically.

To assess the effect of a slow-response nitric oxide analyser, we subjected NO_{sim} to first-order low-pass filtering. When NO_{sim} was filtered with a response time of 3 s, which is similar to our chemiluminescence analyser, the pattern of NO_{meas} along the inspiratory system was well traced for CFS and PGIS (fig. 6). We conclude that since nitric oxide concentrations are usually measured with slow-response analysers with a response time of 3–15 s (e.g. chemiluminescence or electrochemical cell), depending on the site and tidal volume, NO_{meas} could represent any concentration between the true maximum or minimum of the nitric oxide dilution curve along the inspiratory system. Our simulation showed that near the "Y" piece, NO_{true} may be twice as high as NO_{meas} despite mixing along the inspiratory system.

The simulation model we used has certain limitations. We used a mixing chamber model to generate precise information concerning the size and position of peaks and troughs of nitric oxide concentration along the inspiratory system. Mixing chamber models assume instantaneous mixing between two contiguous volume elements and thus ignore the time-dependent aspect of mixing. Other models,[22] such as diffusion with drift or local density random walk could have been used. Validation of simulated models is a general problem because no precise measurement of nitric oxide concentration with an adequate time resolution is possible. Thus we chose to validate our model after low-pass filtering of NO_{sim} in order to take account of the effect of the response time of the measurement device. As the NO_{meas} profile along the inspiratory system was well traced (fig. 6), our mixing chamber model was useful to obtain additional information on mixing of nitric oxide–nitrogen with inspired gas in patients undergoing ventilation. In addition, we analysed the effect of a delay in the delivery of nitric oxide–nitrogen for PGIS. At present, the simulation does not include features to simulate a non-linear behaviour of the nitric oxide delivery device. We have found non-linearity for the Pulmonox-Mini and this is probably the reason why NO_{meas} was less than NO_{filter} for PGIS (fig. 6, right lower panel).

Although nitric oxide is still an experimental drug, nitric oxide inhalation therapy is already used widely for ARDS, pulmonary hypertension and right ventricular failure. Cautious recommendations for its use have been published.[1 18 21 23-26] We found that during controlled ventilation, only the Nodomo generated homogeneous nitric oxide mixtures. CFS generated more inhomogeneous nitric oxide mixtures, especially at high tidal volumes, but offered two major advantages: it was simple to use and independent of power sources. PGIS generated more homogeneous nitric oxide mixtures, but their performances were affected by factors such as dynamic flow measurement and a technically inherent delay between flow measurement and addition of nitric oxide–nitrogen. Because PGIS and CFS may generate inhomogeneous nitric oxide mixtures, it is advisable to inject nitric oxide–nitrogen near the ventilator and to use the inspiratory system to improve mixing.

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References

1. Zapol WM, Rimar S, Gillis N, Marletta M, Bosken CH. Nitric oxide and the lung. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: 1375–1380.
2. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *New England Journal of Medicine* 1993; **328**: 399–405.
3. Kinsella JP, Neish SR, Ivy DD, Shaffer E, Abman SH. Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of inhaled nitric oxide. *Journal of Pediatrics* 1993; **123**: 103–108.
4. Girard C, Lehot JJ, Pannetier JC, Filley S, Ffrench P, Estanove S. Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary artery hypertension. *Anesthesiology* 1992; **77**: 880–883.
5. Westfelt UN, Lundin S, Stenqvist O. Nitric oxide administration after the ventilator: evaluation of mixing conditions. *Acta Anaesthesiologica Scandinavica* 1997; **41**: 266–273.
6. Sydow M, Bristow F, Zinserling J, Allen SJ. Variation of nitric oxide concentration during inspiration. *Critical Care Medicine* 1997; **25**: 365–371.
7. Tibballs J, Hochmann M, Carter B, Osborne A. An appraisal of techniques for administration of gaseous nitric oxide. *Anaesthesia and Intensive Care* 1993; **21**: 844–847.
8. Cuthbertson BH, Stott S, Webster NR. Use of inhaled nitric oxide in British intensive therapy units. *British Journal of Anaesthesia* 1997; **78**: 696–700.
9. Krebs C, Escuyer M, Urak G, Zimpfer M, Germann P. Technological basis for NO application and environmental security. *Acta Anaesthesiologica Scandinavica Supplement* 1996; **109**: 84–87.
10. Lindberg L, Rydgren G, Larsson A, Olsson SG, Nordström L. A delivery system for inhalation of nitric oxide evaluated with chemiluminescence, electrochemical fuel cells, and capnography. *Critical Care Medicine* 1997; **25**: 190–196.
11. Young JD, Roberts M, Gale LB. Laboratory evaluation of the I-NOvent nitric oxide delivery device. *British Journal of Anaesthesia* 1997; **79**: 398–401.
12. Mourgeon E, Gallart L, Umamaheswara Rao GS, Lu Q, Law-Koune JD, Puybasset L, Coriat P, Rouby JJ. Distribution of inhaled nitric oxide during sequential and continuous administration into the inspiratory limb of the ventilator. *Intensive Care Medicine* 1997; **23**: 849–858.
13. Moors AH, Pickett JA, Mahmood N, Latimer RD, Oduro A. Nitric oxide administration. *Anaesthesia and Intensive Care* 1994; **22**: 310–312.
14. Imanaka H, Hess D, Kirmse M, Bigatello LM, Kacmarek RM, Steudel W, Hurford WE. Inaccuracies of nitric oxide delivery systems during adult mechanical ventilation. *Anesthesiology* 1997; **86**: 676–688.
15. Hiesmayr M, Frey B, Laßnigg A, Kastner J, Mares P, Haider W. Emergency nitric oxide inhalation dosage: the critical role of expiratory time, site of application and measurement. *American Journal of Respiratory and Critical Care Medicine* 1996; **153**: A376.
16. Foubert L, Mareels K, Fredholm M, Lundin S, Stenqvist O A study of mixing conditions during nitric oxide administration using simultaneous fast response chemiluminescence and capnography. *British Journal of Anaesthesia* 1997; **78**: 436–438.
17. Sydow M, Bristow F, Zinserling J, Allen SJ. Flow-proportional administration of nitric oxide with a new delivery system: Inspiratory nitric oxide concentration fluctuation during different flow conditions. *Chest* 1997; **112**: 496–504.
18. Young JD, Dyar OJ. Delivery and monitoring of inhaled nitric oxide. *Intensive Care Medicine* 1996; **22**: 77–86.
19. Bohl W. *Technische Strömungslehre*. 10th Edn. Wurzburg; Germany: Vogel, 1994.
20. Gardner FM, Baker JD. Feedback loops and control signals. In: *Simulation Techniques: Models of Communication Signals and Processes*. New York: John Wiley and Sons, 1997; 420–421.
21. Bigatello LM, Zapol WM. New approaches to acute lung injury. *British Journal of Anaesthesia* 1996; **77**: 99–109.
22. Meier P, Zierler KL. On the theory of the indicator-dilution method for measurement of blood flow and volume. *Journal of Applied Physiology* 1954; **6**: 731–744.
23. Body SC, Hartigan PM, Shernan SK, Formanek V, Hurford WE. Nitric oxide: delivery, measurement, and clinical application. *Journal of Cardiothoracic and Vascular Anesthesia* 1995; **9**: 748–763.
24. Frostell CG, Zapol WM. Inhaled nitric oxide, clinical rationale and applications. *Advances in Pharmacology* 1995; **34**: 439–456.
25. Fullerton DA, McIntyre RC jr. Inhaled nitric oxide: therapeutic applications in cardiothoracic surgery. *Annals of Thoracic Surgery* 1996; **61**: 1856–1864.
26. Rossaint R, Busch T, Falke K. Nitric oxide inhalation therapy in acute respiratory distress syndrome: intended effects and possible side effects *Methods in Enzymology* 1996; **269**: 442–453.

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Effects of dantrolene on the diaphragm muscle of the normal and myopathic hamster

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Summary

Dantrolene is the only known effective treatment for malignant hyperthermia. However, its effects on the myopathic diaphragm remain unknown. The effects of dantrolene 10^{-8} to 10^{-4} mol litre^{-1} on diaphragm muscle strips in normal (n=12) and myopathic hamsters (n=13) were investigated *in vitro* in response to tetanic stimulation. We studied contraction under isotonic and isometric conditions. Data are presented as mean (SD) percent of baseline. Dantrolene induced a negative inotropic effect in normal and myopathic hamsters but no significant difference was observed between groups (active force at 10^{-4} mol litre^{-1}: 34 (7) *vs* 32 (11) %; ns). We conclude that dantrolene induced a comparable negative inotropic effect on diaphragm muscle in normal and myopathic hamsters. (*Br. J. Anaesth.* 1998; **81**: 553–555).

Keywords: pharmacology, dantrolene; malignant hyperthermia; muscle, diaphragm; hamster

Dantrolene is a postsynaptic skeletal muscle relaxant that inhibits calcium release from the sarcoplasmic reticulum (SR), by either direct or indirect interaction with skeletal muscle Ca^{2+} release channel of the SR (i.e. ryanodine receptor).[1] Thus dantrolene is the only known effective treatment for malignant hyperthermia (MH).[2] However, dantrolene induces a negative inotropic effect on normal skeletal and diaphragm muscles, but the effects of dantrolene on myopathic muscles remain unknown. Genetically induced myopathy in the Syrian hamster offers a unique opportunity to compare the pharmacological effects of drugs in normal and myopathic muscles. Indeed, the myopathic Syrian hamster is used widely as an animal model as it develops both autosomal recessive cardiomyopathy and polymyopathy that have been well characterized.[3 4] Therefore, we conducted an *in vitro* study on the effects of dantrolene on diaphragm muscle in normal and myopathic hamsters.

Materials and methods

Care of the animals conformed to the recommendations of the Helsinski Declaration, and the study was performed in accordance with the regulations of the official edict of the French Ministry of Agriculture. Experiments were conducted using 13, 6-month-old myopathic Syrian hamsters (Strain Bio 14.6, Bio Breeders Inc., Fitchburg, MA, USA) and 12 normal Syrian hamsters (Strain F1B, Bio Breeders Inc.). Myopathic hamsters of both sexes develop generalized myopathy from the age of 6 weeks.[3 4]

After brief anaesthesia with ether, a muscle strip from the ventral costal diaphragm was dissected carefully from the muscle *in situ*.[4] This diaphragm strip was immediately suspended vertically in a 200-ml jacketed reservoir, maintained at 29°C with a thermostatic water circulator, with Krebs–Henseleit bicarbonate buffer solution ($CaCl_2$ 2.5 m mol litre^{-1}, pH 7.40). The bathing solution was bubbled with 95% oxygen–5% carbon dioxide. Preparations were field-stimulated by means of two platinum electrodes. Experiments were conducted after a 30-min stabilization period, at the initial muscle length at the apex of the length-active isometric tension curve (*l*max), in tetanus mode at 50 Hz (10 trains min^{-1} of 300 ms duration, 1 ms rectangular pulses). Cross-sectional area was calculated from the ratio of muscle weight to muscle length, assuming a muscle density of 1.

Because dantrolene is poorly soluble in aqueous media, we used dimethylsulphoxide (DMSO) as a solvent. Therapeutic concentrations of dantrolene range from 0.3 to 10 mg ml^{-1} (1–30x10^{-6} mol litre^{-1}).[5] Therefore, five concentrations of dantrolene were tested in a cumulative manner: 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5} and 10^{-4} mol litre^{-1}, with a 15-min period between each concentration. In a preliminary study, we observed that the effects of the highest concentration of dantrolene remained stable between 15 and 60 min, and that DMSO alone had no significant effect. All drugs were purchased from Sigma-Aldrich Chimie (L'Isle d'Abeau Chesnes, France).

MECHANICAL PARAMETERS

The electromagnetic lever system has been described previously.[4] Briefly, the load applied to the muscle was determined using a Servo mechanism-controlled current through the coil of an electromagnet. Muscular shortening induced displacement of the lever, which modulated the light intensity of a photo-

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electric transducer. The initial preload which determined $l$max, was automatically maintained constant throughout the experiment. All analyses were made from digital records of force and length obtained with a computer.[4]

Parameters characterizing contraction were shortening velocity (vc), extent of shortening (Δl), peak of the positive force derivative normalized per cross-sectional area (+dFdt^{-1}) and active force normalized per cross-sectional area (AF). Mechanical variables were calculated from three consecutive tetanic contractions preloaded at $l$max with increasing afterload from zero load to fully isometric contraction. The first contraction was clamped abruptly to zero load just after the electrical stimulus, enabling determination of the maximum unloaded shortening velocity ($v$cmax). The second contraction was isotonic and loaded with preload only. The maximum extent of shortening (Δlmax) was determined from this contraction. The last contraction was fully isometric at $l$max. The maximum active force (AFmax) and the peak of the positive (+dFdt^{-1}max) force derivative were determined from this fully isometric contraction.

STATISTICAL ANALYSIS

Data are expressed as mean (SD). Comparisons of control values between groups were performed using the Student's t test. Comparison of several means were performed using repeated-measure analysis of variance and Newman–Keuls test. All P values were two-tailed, and $P<0.05$ was considered significant. Statistical analysis was performed using NCSS 6.0 software (Statistical Solutions Ltd, Cork, Ireland).

Results

Body weight was lower in myopathic hamsters than in controls (100 (4) *vs* 144 (5) g; $P<0.05$). There was no significant difference in $l$max between groups (9.6 (1.7) *vs* 9.6 (2.1) mm; ns). Under control conditions, mechanical variables testing inotropy were significantly impaired in myopathic hamsters compared with normal hamsters: Δlmax: 20 (5) *vs* 34 (7) %$l$max ($P<0.05$); $v$cmax: 1.4 (0.5) *vs* 4.5 (0.5) $l$max s^{-1} ($P<0.05$); AFmax: 66 (27) *vs* 101 (37) mN mm^{-2} ($P<0.05$); +dFdt^{-1}max: 745 (350) *vs* 1314 (525) mN mm^{-2} s^{-1} ($P<0.05$).

In normal and myopathic hamsters, dantrolene induced a significant and concentration-dependent negative inotropic effect in diaphragmatic muscle under low ($v$cmax) and high (AFmax) loads. At a concentration of 10^{-4} mol litre^{-1}, dantrolene induced a maximum decrease in AFmax and $v$cmax in normal hamsters (34 (7) % of baseline ($P<0.01$) and 47 (7) % of baseline ($P<0.05$)) and in myopathic hamsters (32 (11) % of baseline ($P<0.01$) and 46 (10) % of baseline ($P<0.05$)). There were no significant differences in the inotropic effects of dantrolene between normal and myopathic hamsters (fig. 1). As baseline values of AF were markedly reduced in myopathic compared with normal hamsters, the absolute values of AF after dantrolene administration in myopathic hamsters were very low (fig. 1).

Discussion

We have studied the effects of dantrolene on the intrinsic contractility of isolated diaphragm muscle in normal and myopathic hamsters. The negative inotropic effect of dantrolene was comparable in normal and myopathic hamsters.

Dantrolene induced a significant and concentration-dependent negative inotropic effect in the normal hamster with a plateau between 10^{-5} and 10^{-4} mol litre^{-1} (fig. 1). Moreover, the maximum decrease in AFmax was similar to the maximum decrease in adductor pollicis muscle force after administration of dantrolene in humans.[5] These results suggest that our experimental model was clinically relevant. There were no significant differences in the negative inotropic effects of dantrolene between normal and myopathic hamsters (fig. 1). The negative inotropic effect of dantrolene on skeletal muscle is thought to be related to its effect on calcium release from the SR. Our results suggest that the effects of dantrolene on the ryanodine receptor complex are similar in normal and myopathic hamsters. Nevertheless, as contraction was markedly impaired in myopathic hamsters, it should be noted that the absolute values of AFmax after dantrolene in myopathic hamsters were very low. Therefore, whereas the pharmacological effects of dantrolene are not modified in myopathic muscle, its consequences on an

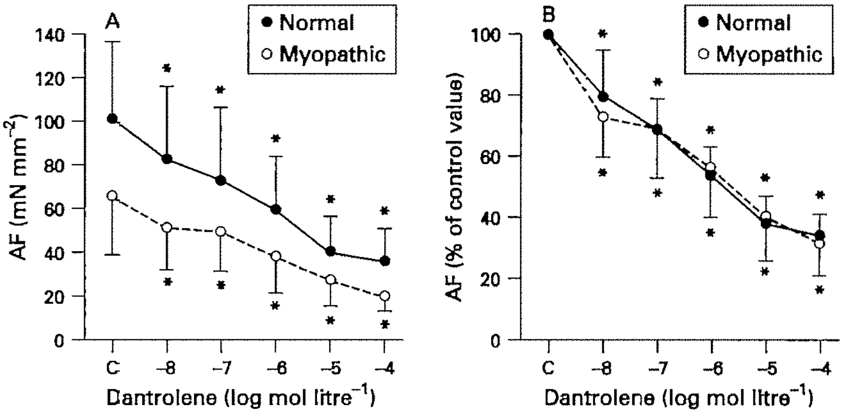

Figure 1 Effects of dantrolene on active isometric force (AFmax) of diaphragmatic muscles from normal and myopathic hamsters muscles. A: Data are absolute values (SD) ($P<0.05$ between groups). B: Data are mean (SD) percentage of baseline (no significant differences between groups). *$P<0.05$ *vs* control (C).

already impaired ventilatory function may be greater (fig. 1). Dantrolene may also affect breathing pattern in decreasing tidal volume while minute ventilation is maintained by increasing ventilatory frequency.[6]

The following points must be considered in the assessment of the clinical relevance of our results. First, this study was conducted at 29°C. However, it should be pointed out that the inotropic effect of dantrolene observed in our study was comparable with that observed *in vivo* in humans at 37°C.[5] Second, the cardiomyopathic Syrian hamster provides a useful and reproducible model of muscle disease, with early development of focal myolytic and necrosis lesions in skeletal and diaphragmatic muscles,[3] that mimic those observed in human muscle dystrophies.[3] Thus this animal model seems to be relevant for the assessment of the effects of dantrolene on myopathic diaphragm function.

In summary, in this study conducted on isolated diaphragm muscle in response to tetanic stimulation, dantrolene induced a comparable negative inotropic effect in normal and myopathic muscles and may be responsible for a diaphragmatic dysfunction.

References

1 Van Winkle WB. Calcium release from skeletal muscle sarcoplasmic reticulum: Site of action of dantrolene sodium? *Science* 1976; **193**: 1130–1131.

2. Kolb ME, Horne ML, Martz R Dantrolene in human malignant hyperthermia. *Anesthesiology* 1982; **56**: 254–262

3. Burbach JA, Schlenker EH, Johnson JL. Morphometry, histochemistry, and contractility of dystrophic hamster diaphragm. *American Journal of Physiology* 1987, **253**: R275–284

4 Coirault C, Chemla D, Pourny JC, Lambert F, Riou B, Lecarpentier Y. Relaxation is impaired in the diaphragm muscle of cardiomyopathic Syrian hamster. *American Journal of Respiratory and Critical Care Medicine* 1997; **155**. 1575–1582.

5. Flewellen EH, Nelson TE, Jones WP, Arens JF, Wagner DL. Dantrolene dose response in awake man: Implications for management of malignant hyperthermia *Anesthesiology* 1983; **59**: 275–280

6. Ellis KO, Wessels FL, Carpenter JF. Effects of intravenous dantrolene sodium on respiratory and cardiovascular functions. *Journal of Pharmaceutical Science* 1976, **65**: 1359–1364.

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Critical haemoglobin concentration in anaesthetized dogs: comparison of two plasma substitutes

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Summary

We have explored systemic and regional tolerance to haemodilution during anaesthesia with two different synthetic colloids. Eighteen dogs undergoing mechanical ventilation during anaesthesia with ketamine were submitted to progressive normovolaemic haemodilution with either gelatin (GEL; *n*=9) or hydroxyethylstarch (HES; *n*=9) administered on a 1:1 ratio. Systemic oxygen delivery was calculated from measurement of thermodilution cardiac output and arterial oxygen content, while systemic oxygen consumption was determined from expired gas analysis. Mesenteric oxygen delivery and consumption were determined using ultrasonic flow measurements, and arterial and mesenteric venous oxygen contents. The critical haemoglobin concentration (i.e. the haemoglobin value below which oxygen consumption becomes oxygen delivery dependent) was mean 3.6 (SD 0.8) g dl^{-1} in the GEL and 3.5 (1.5) g dl^{-1} in the HES group. The mesenteric critical oxygen extraction ratio (O_2ER) (GEL 50.1 (12.1) %; HES 48.5 (13.4) %) was significantly lower than the systemic critical O_2ER (GEL 66.1 (8.4) %; HES 67.7 (7.1) %). There were no significant differences between the GEL and HES groups for any of these variables, or in the amount of colloid administered. During the study, oxygen delivery decreased almost linearly with reduction in haemoglobin, indicating a lack of cardiac output response to anaemia during ketamine anaesthesia. (*Br. J. Anaesth.* 1998; **81**: 556–562)

Keywords: anaesthetics i.v., ketamine; blood, haemodilution; blood, haemoglobin; oxygen, transport; blood, replacement; dog

Increased awareness of the risks associated with allogenic blood has stimulated re-examination of the benefit–risk relationship for transfusion therapy. A better knowledge of the physiology and effect of anaemia during and after surgery has allowed a re-evaluation of the "magic" value of 30%[1 2] during these periods.

However, several important questions remain regarding patient tolerance to acute normovolaemic anaemia. First, the critical concentration of haemoglobin (i.e. the haemoglobin value below which oxygen delivery becomes insufficient to meet tissue oxygen demand in the anaesthetized individual) has not been well defined. Two major mechanisms allow maintenance of adequate oxygen transport to the tissues: an increase in cardiac output and an increase in tissue oxygen extraction. The increase in cardiac output during haemodilution has been well documented in awake and lightly anaesthetized individuals.[3–11] During mild haemodilution, the increase in cardiac output may overcompensate for the decrease in arterial content, so that oxygen transport may increase.[12] However, the ability of the organism to increase oxygen extraction under these conditions has been less well defined. Determination of the critical haemoglobin concentration during normovolaemic haemodilution allows participation of both mechanisms in the maintenance of adequate tissue oxygenation to be explored.[13] Second, redistribution of blood flow during normovolaemic haemodilution from the splanchnic area to the heart and brain has been well described,[14–16] but the ability of the splanchnic area to extract oxygen during haemodilution has not been well defined. Third, the physicochemical properties of synthetic colloids used to maintain stable volume expansion during acute anaemia may influence the critical haemoglobin concentration in these conditions.

Among the different available synthetic colloids, gelatin (GEL) and hydroxyethylstarch (HES) solutions are the most commonly used. Gelatins, obtained from degradation of collagen, have a limited volume expansion effect and a short intravascular half-life.[17 18] They have the advantages of excellent tolerance and low cost, but are associated with a relatively high incidence of anaphylactoid reactions, especially with urea-linked gelatins.[19] HES solutions are modified natural polysaccharides, which have a better volume expansion effect than gelatins.[20 21] Low molecular weight HES solutions are characterized by a shorter intravascular half-life and a smaller incidence of side effects than high molecular weight HES solutions.[20–22]

In this study, we have explored systemic and regional tolerance to progressive normovolaemic haemodilution in anaesthetized dogs using either a

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modified fluid gelatin or low molecular weight HES. Ketamine anaesthesia was chosen as this agent has well known cardiostimulant properties,[23] and has the least deleterious effects on tissue oxygen extraction capabilities.[24]

Materials and methods

All experimental procedures were performed according to the NIH guidelines and were approved by our Animal Ethics Care Committee. We studied 18 mongrel dogs (weight 21.9±4.5 kg). After administration of thiopental 20 mg kg^{-1} i.v., tracheal intubation was performed and mechanical ventilation started on control mode (Elema 900 B, Siemens, Solna, Sweden) with air ($F\text{I}_{\text{O}_2}$=0.21). Ventilatory frequency was set at 12 bpm and tidal volume was adapted to obtain $P\text{a}_{\text{CO}_2}$ at 4.6–5.3 kPa. Respiratory conditions remained unchanged until the end of the study. Anaesthesia was maintained with an i.v. bolus dose of ketamine 10 mg kg^{-1}, followed by continuous infusion of 0.4 mg kg^{-1} min^{-1}. Neuromuscular block was achieved with pancuronium at an initial dose of 0.1 mg kg^{-1}, followed by hourly boluses of 1–2 mg.

Electrodes were attached to the four limbs for monitoring heart rate. Two catheters (16G, Becton Dickinson and CO, Rutherford, NJ) were inserted, one into a peripheral vein for fluid and drug infusions, and one into the distal aorta via a femoral artery for monitoring arterial pressure and sampling arterial blood. A pulmonary artery catheter (Swan–Ganz catheter model 93A-131-7F, Baxter Healthcare, Irvine, CA, USA) was inserted via a jugular vein into the pulmonary artery. A gas analyser (Capnomac AGM-103, Datex, Helsinki, Finland) was inserted in the respiratory breathing system for monitoring end-expired carbon dioxide concentration ($P\text{E}'_{\text{CO}_2}$). Exhaled gases were directed through a mixing chamber for sampling. The expired oxygen fraction ($F\text{E}'_{\text{CO}_2}$) was measured continuously by a semi-rapid gas analyser (model 500D PK, Morgan Co, Chatham, UK).

A splenectomy was performed via a midline laparotomy to prevent blood autotranfusion. During laparotomy, ultrasonic flow probes (Transonic Systems Inc., Ithaca, NY, USA) were inserted, one around the mesenteric artery and one around the left renal artery. A third probe was inserted around the remaining femoral artery, through a small cutaneous incision. Mesenteric, renal and femoral blood flows were measured with a flowmeter (model T208, Transonic Systems Inc., Ithaca, NY, USA; calibration performed by the manufacturer). In seven dogs in each group, an 18-gauge catheter (Becton Dickinson and CO, Rutherford, NJ) was inserted in the mesenteric vein via a peripheral branch. To compensate for insensible losses, the dogs received i.v. infusion of 0.9% NaCl at a rate of 10 ml kg^{-1} during splenectomy and 1 ml kg^{-1} h^{-1} thereafter, until the end of the experiment.

Heart rate, arterial pressure and pulmonary artery pressure were monitored continuously (Sirecust, Siemens AG, Erlangen, Germany) and recorded together with $P\text{E}'_{\text{CO}_2}$ and $F\text{E}'_{\text{CO}_2}$ (model 8000S, Gould Electronique, Ballainvilliers, France); zero pressure was set at the mid-chest level of the animal. Body temperature was maintained at 36–38°C throughout the study, using warming blankets and humidified heated gases.

Heart rate (HR) and intravascular pressures, including mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), right atrial pressure (RAP) and pulmonary artery occlusion pressure (PAOP) were measured at end-expiration from the paper trace. $P\text{E}'_{\text{CO}_2}$ and $F\text{E}'_{\text{CO}_2}$ were measured from the paper trace over 1 min. Expired volume was measured with a spirometer (model Magtrak II, London, UK) over the same period. After measurement of mesenteric, renal and femoral blood flows, cardiac output (CO) was measured by the thermodilution technique (module E 2261/A, Siemens AG, Erlangen, Germany) by repeated injections of 10 ml of cold (<5°C) 5% glucose in water. Each injection was started at the end of inspiration. Three to five measurements, with a variability of less than 10%, were averaged for each measurement of CO. Immediately thereafter, arterial, mixed venous and mesenteric blood samples were withdrawn for measurement of blood-gas tensions (ABL 2, Radiometer, Copenhagen, Denmark). Haemoglobin concentration and saturation were measured using a co-oximeter (OSM3, Radiometer, Copenhagen, Denmark). Each sample was analysed twice and the two consecutive values averaged. Blood lactate concentration was measured enzymatically using an automated analyser (Kontron, Basel, Switzerland).

Cardiac index (CI), stroke index (SI), systemic and pulmonary vascular resistance (SVR, PVR), left and right ventricular stroke work index (LVSWI, RVSWI) and oxygen delivery ($D\text{O}_2$) were calculated using the following formulae:

$\text{CI (ml min}^{-1}\text{ kg}^{-1}\text{)=CO/weight}$
$\text{SI (ml kg}^{-1}\text{)=CI/HR}$
$\text{SVR (dyn s cm}^{-5}\text{)=79.9}\times\text{(MAP–RAP)/CO}$
$\text{PVR (dyn s cm}^{-5}\text{)=79.9}\times\text{(MPAP–PAOP)/CO}$
$\text{LVSWI (g m kg}^{-1}\text{)=0.0136}\times\text{(MAP–PAOP)}\times\text{SI}$
$\text{RVSWI (g m kg}^{-1}\text{)=0.0136}\times\text{(MPAP–RAP)}\times\text{SI}$
$D\text{O}_2\text{ (ml min}^{-1}\text{ kg}^{-1}\text{)=CI}\times C\text{a}_{\text{O}_2}\times 10$

where $C\text{a}_{\text{O}_2}$=oxygen content of arterial blood.

Oxygen consumption $\dot{V}\text{O}_2$ (ml min^{-1} kg^{-1}) was calculated from measured $F\text{E}'_{\text{CO}_2}$ and minute ventilation, using the appropriate mass balance equation indexed for weight.[25] Oxygen extraction ratio (O_2ER) was obtained by dividing $\dot{V}\text{O}_2$ by $D\text{O}_2$.

Mesenteric oxygen delivery ($D\text{O}_2$m) was determined from the product of mesenteric blood flow and arterial oxygen content, while mesenteric oxygen consumption ($\dot{V}\text{O}_2$m) was obtained by the product of mesenteric blood flow and the difference between arterial and venous mesenteric oxygen contents. Mesenteric oxygen extraction (O_2ERm) was calculated as:

$(C\text{a}_{\text{O}_2}–C\text{m}_{\text{O}_2})/C\text{a}_{\text{O}_2}$

where $C\text{m}_{\text{O}_2}$=oxygen content of mesenteric venous blood.

Thirty minutes after completion of the surgical procedure, the dogs were allocated randomly to one of two groups of nine dogs each, according to the plasma substitute used in the subsequent haemodilution procedure. After baseline measurements, each animal was slowly haemodiluted by repeated withdrawals of 5-ml kg^{-1} aliquots of arterial blood simultaneously replaced by the same volume of either 3% modified fluid gelatin (Geloplasma, Propharm, France) (GEL group; n=9) or 6% hydroxyethylstarch 200/0.5 (Haes-Stéril 6%, Fresenius AG, Bad Homburg, Germany) (HES group; n=9). After each exchange procedure, a 15-min period was allowed to reach a new steady state defined by stable mean arterial pressure, heart rate, $P\mathrm{E}'_{\mathrm{CO}_2}$ and $F\mathrm{E}'_{\mathrm{CO}_2}$. Then a new set of measurements was performed. In an attempt to maintain normovolaemia during the progressive haemodilution, PAOP was measured after each exchange procedure and maintained at least at the baseline level by additional infusion (1–2 ml kg^{-1}) of the allocated colloid.

The exchange procedure was continued until the animal could no longer maintain a stable arterial pressure. Death followed shortly thereafter, with the animal still anaesthetized.

STATISTICAL ANALYSIS

In each animal, critical $D\mathrm{o}_2$ ($D\mathrm{o}_2$crit) was determined from a plot of $\dot{V}\mathrm{o}_2$ *vs* $D\mathrm{o}_2$ using the dual lines regression method.[26] $D\mathrm{o}_2$crit was defined as the point of intersection of the two best-fit regression lines as determined by a least sum of squares technique. Critical O_2ER (O_2ERcrit) was calculated as the ratio of $\dot{V}\mathrm{o}_2/D\mathrm{o}_2$ at $D\mathrm{o}_2$crit. $D\mathrm{o}_2$crit was also determined in each animal using the same dual regression lines analysis from a plot of blood lactate *vs* $D\mathrm{o}_2$. This value was called $D\mathrm{o}_2$crit(Lac). The critical value of haemoglobin (Hbcrit), defined as the value of haemoglobin below which $\dot{V}\mathrm{o}_2$ began to decrease, was determined using the same mathematical analysis, from a plot of haemoglobin *vs* $\dot{V}\mathrm{o}_2$.

In the seven animals in each group where a mesenteric venous catheter was inserted, the mesenteric $D\mathrm{o}_2/\dot{V}\mathrm{o}_2$ relationship was analysed similarly, from a plot of $\dot{V}\mathrm{o}_2$m *vs* $D\mathrm{o}_2$m. In each animal, the systemic haemoglobin/$D\mathrm{o}_2$ relationship was also analysed, by determining the polynomial that best fitted the data. From these polynomials, $D\mathrm{o}_2$ values corresponding to standardized haemoglobin values were obtained and compared between the two groups.

In both groups, haemodynamic and respiratory variables, including regional blood flow, obtained at baseline and at the experimental point closest to critical $D\mathrm{o}_2$ were compared using two-way analysis of variance (time and group), followed by a Tukey test for pairwise comparisons when statistically significant. Critical values of $D\mathrm{o}_2$ and haemoglobin, volume of blood withdrawn and volume of colloid adminis-

Table 1 Haemodynamic and oxygen derived data obtained at baseline and near the critical point in the gelatine haemodiluted dogs (group GEL, n=9) and in the hydroxyethylstarch haemodiluted dogs (group HES, n=9) (see text for details). *P<0.05, **P<0.01 *vs* baseline; †P<0.05 HES *vs* GEL

	Group	Baseline	Near critical point
Temperature (°C)	GEL	37.5 (1.2)	36.5 (1.7)
	HES	37.8 (1.0)	36.6 (1.8)
HR (beat min^{-1})	GEL	158 (19)	120 (28) **
	HES	164 (35)	134 (31) *
MAP (mm Hg)	GEL	105 (16)	52 (18) **
	HES	113 (31)	71 (16) **
PAPm (mm Hg)	GEL	12.7 (3.8)	10.7 (3.3)
	HES	13.9 (2.3)	12.9 (2.8)
PAOP (mm Hg)	GEL	3.2 (1.8)	3.9 (2.0)
	HES	3.4 (1.3)	4.1 (1.4)
RAP (mm Hg)	GEL	2.1 (1.6)	2.9 (2.0)
	HES	1.7 (0.6)	2.6 (1.8)
CI (ml min^{-1} kg^{-1})	GEL	111 (26)	111 (27)
	HES	134 (29)	129 (29)
SI (ml kg^{-1})	GEL	0.71 (0.16)	0.84 (0.35)
	HES	0.85 (0.24)	1.00 (0.30)
SVR (dyn s cm^{-5})	GEL	3498 (1155)	1579 (411) **
	HES	3342 (955)	2215 (805) **
PVR (dyn s cm^{-5})	GEL	411 (131)	340 (91)
	HES	421 (85)	413 (129)
LVSWI (g m kg^{-1})	GEL	0.98 (0.24)	0.61 (0.20) **
	HES	1.21 (0.35)	0.93 (0.40)
RVSWI (g m kg^{-1})	GEL	0.10 (0.06)	0.10 (0.04)
	HES	0.14 (0.03)	0.14 (0.04)
Hb (g dl^{-1})	GEL	14.5 (2.6)	4.0 (0.7) **
	HES	14.7 (3.7)	3.8 (1.8) **
$S\mathrm{a}_{\mathrm{O}_2}$ (%)	GEL	94.4 (2.6)	92.1 (6.7)
	HES	94.4 (1.5)	95.7 (1.6)
$S\mathrm{v}_{\mathrm{O}_2}$ (%)	GEL	72.8 (6.1)	35.6 (7.4) **
	HES	76.1 (4.1)	38.5 (7.2) **
$D\mathrm{o}_2$ (ml min^{-1} kg^{-1})	GEL	21.2 (5.6)	5.9 (1.0) **
	HES	25.7 (7.2)	6.5 (1.8) **
$\dot{V}\mathrm{o}_2$ (ml min^{-1} kg^{-1})	GEL	4.5 (0.5)	3.7 (0.8) *
	HES	5.0 (1.1)	4.2 (1.2)
O_2ER (%)	GEL	22.3 (5.5)	63.8 (10.2) **
	HES	20.1 (3.2)	65.4 (12.0) **
Lactate (mmol litre^{-1})	GEL	2.4 (0.9)	5.1 (2.5) **
	HES	2.2 (0.9)	2.1 (1.0)†
$P\mathrm{E}'_{\mathrm{CO}_2}$ (mm Hg)	GEL	26.6 (4.4)	25.6 (7.7)
	HES	26.9 (3.5)	24.0 (5.3)

tered to reach the critical point were compared between groups using the Mann–Whitney *U* test. Data obtained from the mesenteric $Do_2/\dot{V}o_2$ relationship were also compared between groups using the Mann–Whitney *U* test. In both groups, O_2ERcrit and O_2ERm were compared using the Wilcoxon rank test.

The systemic haemoglobin/Do_2 relationship was analysed using two-way analysis of variance for repeated measurements. In each group the Do_2 value for a haemoglobin concentration below baseline was compared with the Do_2 value obtained for baseline haemoglobin (i.e. 13.0 g dl^{-1}) by a method of contrasts.

All values are expressed as mean (SD). $P<0.05$ was considered significant.

Results

HAEMODYNAMIC AND RESPIRATORY EFFECTS OF HAEMODILUTION (TABLE 1)

In both groups, progressive haemodilution was associated with a slight decrease in blood temperature (ns). HR and MAP decreased significantly. PAOP and RAP tended to increase (ns). CI did not change while SI tended to increase. SVR decreased, as did LVSWI. The decrease in arterial oxygen content resulted in a significant decrease in oxygen delivery. As CO did not increase during haemodilution, systemic oxygen delivery decreased in parallel to the decrease in haemoglobin (fig. 1). Despite a marked increase in oxygen extraction ratio, oxygen consumption also decreased, although this was significant only in the GEL group. The effects of haemodilution were similar in both groups, except for blood lactate, which increased significantly only in the GEL group. There was no group–time interaction for all investigated variables.

EFFECTS OF HAEMODILUTION ON CRITICAL DO_2 AND CRITICAL HAEMOGLOBIN CONCENTRATION (TABLE 2)

Figure 2 shows the $Do_2/\dot{V}o_2$ and haemoglobin/$\dot{V}o_2$ relationships in one representative dog from each group. There was no significant difference in Do_2crit, $\dot{V}o_2$crit or O_2Ercrit between the two groups. Do_2crit obtained from blood lactate measurements was also similar in both groups, although blood lactate at the critical point was significantly higher in the GEL group than in the HES group. There was no significant difference in the critical haemoglobin concentration (table 2).

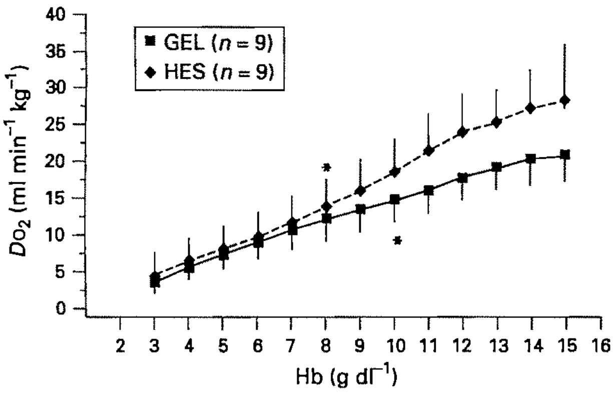

Figure 1 Haemoglobin (Hb)/Do_2 relationship in the GEL and HES groups. *Significantly different from baseline Do_2 (Do_2 for a haemoglobin concentration of 15.0 g dl kg^{-1}).

Table 2 Data at the critical point in the GEL and HES groups

	GEL group (n=9)	HES group (n=9)
Do_2crit (ml min^{-1} kg^{-1})	6.0 (1.2)	4.0 (0 9)
$\dot{V}o_2$crit (ml min^{-1} kg^{-1})	6.3 (1.4)	4.3 (1.1)
O_2ERcrit (ml min^{-1} kg^{-1})	66.1 (8.4)	7.6 (1.3)
Do_2crit (Lac) (ml min^{-1} kg^{-1})	67.7 (7.1)	3.6 (0.8)
Hbcrit (g dl^{-1})	6 6 (1.7)	3.5 (1.5)

There was no significant difference between the two groups in amount of blood withdrawn (GEL 60.7 (19.5) ml kg^{-1}; HES 74.6 (27.5) ml kg^{-1}) or in the amount of colloid administered (GEL 68.3 (19.5) ml kg^{-1}; HES 77.4 (29.4) ml kg^{-1}) to reach the critical point.

REGIONAL EFFECTS OF HAEMODILUTION (TABLE 3)

Progressive haemodilution was associated with an increase in mesenteric blood flow but not in renal and femoral blood flows in both groups. When these regional blood flows were expressed as a fraction of the CO, mesenteric blood flow increased, while renal blood flow tended to decrease and femoral blood flow remained unchanged.

EFFECTS OF HAEMODILUTION ON CRITICAL MESENTERIC DO_2 (TABLE 4, FIG. 3)

There was no significant difference in critical mesenteric blood flow, venous oxygen saturation, Do_2, $\dot{V}o_2$ or O_2ER between the two groups. In both groups, mesenteric O_2ERcrit was significantly lower than global O_2ERcrit ($P<0.02$).

Discussion

We have examined the systemic and regional effects of progressive normovolaemic haemodilution in anaesthetized animals. Although not often used in clinical practice, ketamine was chosen as the anaesthetic agent for its cardiovascular properties[23 27 28] and its effects on tissue oxygen extraction.[24]

We found that the critical haemoglobin concentration in anaesthetized dogs undergoing ventilation with air was 3.5–4 g dl^{-1}. Interestingly, data obtained from analysis of either the haemoglobin/$\dot{V}o_2$ relationship or the $Do_2/\dot{V}o_2$ relationship were identical. The critical haemoglobin concentration we observed is in agreement with two other animal studies. In pentobarbital-anaesthetized dogs,[29] Cain estimated the critical haematocrit concentration to be approximately 10%. In pentobarbital-anaesthetized pigs undergoing progressive haemodilution with dextran 40, Räsänen[30] found a critical haemoglobin value of 3.9 g dl kg^{-1}. Obviously, corresponding values are difficult to obtain in humans. Nevertheless, van Woerkens, Trouwborst and van Lanschot[31] studied a sedated Jehovah Witness patient who died from extreme haemodilution, and observed a critical haemoglobin concentration of 4 g dl kg^{-1}.

At the critical point, whole body oxygen extraction ratio was approximately 60%, a value which is very

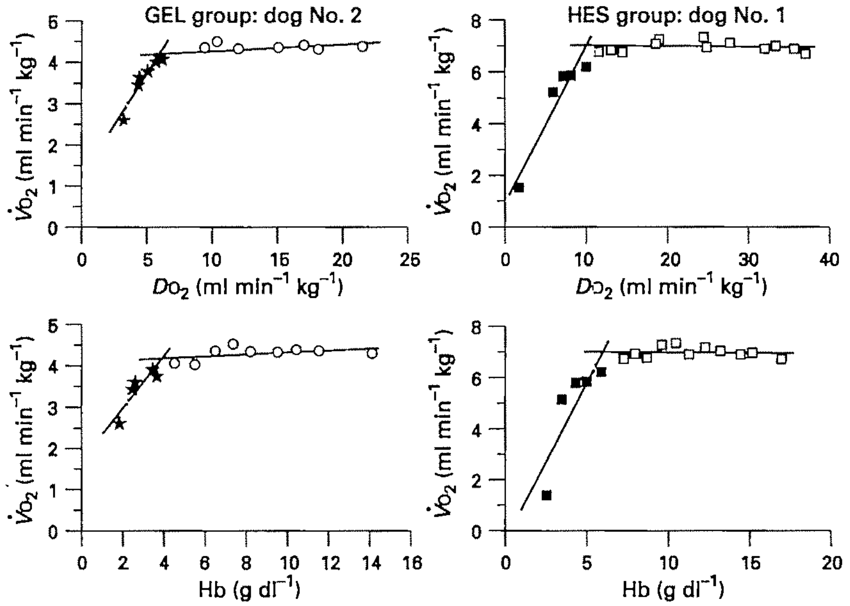

Figure 2 $Do_2/\dot{V}o_2$ (top) and haemoglobin (Hb)/$\dot{V}o_2$ (bottom) relationships in one representative animal from the GEL group (left) and the HES group (right).

similar to that observed during haemorrhagic shock in dogs using the same anaesthetic technique.[24] Critical oxygen delivery and consumption tended to be lower in the haemodilution than in the haemorrhagic protocol, but this could be attributed to the small decrease in body temperature which was unavoidable during massive administration of i.v. fluids.

Progressive haemodilution was associated with redistribution of blood flow to the mesenteric area, but not to the kidneys or muscles. These data are in agreement with other animal studies demonstrating that the kidneys are the organs at risk during haemodilution.[15 32] Using radioactive microspheres, Crystal and Salem[15 32] demonstrated, in pentobarbital-anaesthetized dogs, that haemodilution to a haemoglobin value of 8 g dl kg^{-1} was not associated with an increase in renal blood flow, resulting in a decrease in renal oxygen delivery. Although mesenteric blood flow tended to increase during haemodilution, mesenteric oxygen extraction was significantly lower than systemic oxygen extraction at the critical point. This can be related to alteration of mesenteric oxygen extraction capabilities related to haemodilution. Kiel, Riedel and Shepherd[33] observed in pentobarbital-anaesthetized dogs a reduction in intestinal oxygen extraction during haemodilution which might be attributed to the vascular organization of the intestinal mucosa. In young pigs anaesthetized with ketamine and flunitrazepam, Nöldge and colleagues[34] also observed that haemodilution to a packed cell volume of 14% was associated with a decrease in mean surface Po_2 of the liver and small intestine, indicating that the increases in blood flow and oxygen extraction were no longer able to compensate for the decrease in splanchnic oxygen delivery. At this level of haemodilution, small intestine oxygen extraction was only 33%, while liver oxygen extraction was 49%.

We have also explored the possibility that the physiological modifications associated with normovolaemic haemodilution might be influenced by the type of fluid used for the exchange. In view of the shorter intravascular persistence of gelatin, its volume could have been greater than the volume of HES, but this was not the case, probably because of the short duration of the experiments. Under the conditions of our study, differences between the two solutions were small. These observations are in agreement with a recent study,[35] showing that the *in vivo* rheological effects of these two colloids are similar and less favourable than those of 3.5% dextran 40. The GEL group had a higher blood lactate concentration at the critical point, but this was likely to be

Table 3 Regional blood flows at baseline and near the critical point in the GEL (n=9) and HES (n=9) groups. *P=0.079 *vs* baseline

	Group	Baseline	Near critical point
Mesenteric blood flow (ml min^{-1})	GEL	207 (192)	306 (209)
	HES	192 (101)	277 (102)
Mesenteric blood flow (% of CO)	GEL	7.3 (4.3)	11.1 (4.5) *
	HES	7.2 (4.4)	10.8 (3.6) *
Renal blood flow (ml min^{-1})	GEL	197 (103)	122 (67)
	HES	180 (80)	163 (126)
Renal blood flow (% of CO)	GEL	7.5 (3.1)	5.1 (2.9)
	HES	7.2 (3.3)	6.0 (3.3)
Femoral blood flow (ml min^{-1})	GEL	36 (26)	42 (34)
	HES	56 (30)	51 (21)
Femoral blood flow (% of CO)	GEL	1.3 (0.5)	1.5 (1.0)
	HES	2.0 (0.9)	2.0 (0.8)

Table 4 Mesenteric $Do_2/\dot{V}o_2$ relationship in the GEL and HES groups

	GEL group (n=7)	HES group (n=7)
Do_2crit (ml min^{-1} kg^{-1})	0.660 (0.395)	0.636 (0.294)
$\dot{V}o_2$crit (ml min^{-1} kg^{-1})	0.324 (0.202)	0.281 (0.076)
O_2ERcrit (%)	50.1 (12.1)	48.5 (13.4)
Mesenteric blood flow (ml min^{-1})	240 (168)	295 (147)
Mesenteric $S\bar{v}O_2$ (%)	45.9 (10.8)	56.0 (10.0)

related to the presence of lactate in the gelatin solution.

Interestingly, progressive haemodilution was not associated with an increase in CO in our anaesthetized animals. Similar results were reported in dogs and in humans[4 36 37] during anaesthesia with halogenated anaesthetics, which have known cardiodepressant and sympatholytic effects.[38] Our observations were somewhat surprising as ketamine has sympathomimetic actions related to direct stimulation of central nervous system structures.[27 28] The absence of an increase in CO, despite the decrease in systemic vascular resistance and maintenance of constant cardiac filling pressures, could be related to the negative inotropic properties of ketamine at the dose used in our study,[27 39] as suggested by the decrease in left ventricular stroke work in the presence of a constant PAOP. Previous administration of thiopental at induction of anaesthesia might also have blunted the cardiovascular stimulant properties of ketamine,[40] although we used very small doses of thiopental and the actual procedure started at least 2 h after administration of thiopental. Even more surprising was the significant decrease in HR during haemodilution in our animals. The reason for this decrease is unclear, as ketamine did not seem to increase parasympathetic tone[41] or depress baroreceptor reflex activity.[42] As CO did not increase during progressive haemodilution, oxygen delivery decreased in parallel with the reduction in arterial oxygen content. Therefore, we did not observe the relationship between haemoglobin and oxygen delivery as demonstrated by Messmer and colleagues,[12] showing a maximum oxygen delivery for haemoglobin concentration close to 10 g dl kg^{-1}. Our observations are in agreement with those reported by Cain in pentobarbital-anaesthetized dogs.[29] Therefore, ketamine, in common with halogenated anaesthetics, may limit the ability of the organism to tolerate severe haemodilution.

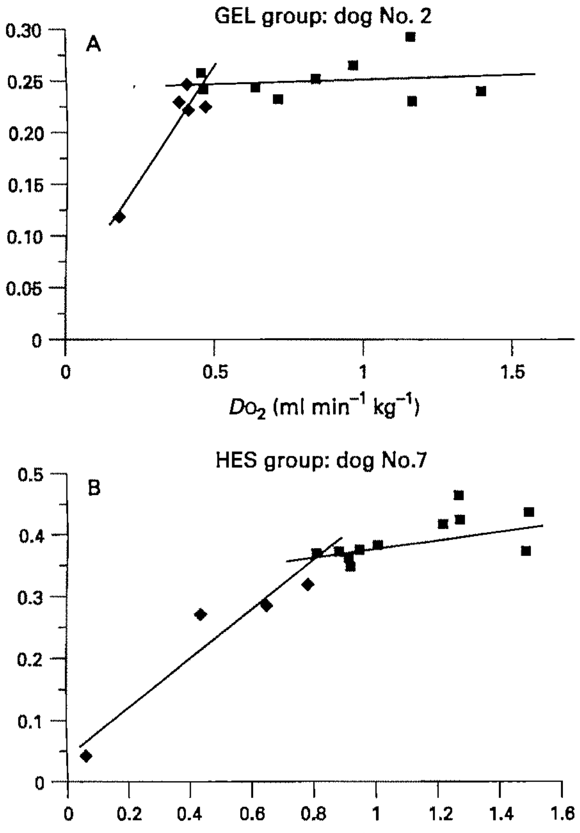

Figure 3 Mesenteric $Do_2/\dot{V}o_2$ relationship in one representative dog from the GEL group (A) and from the HES group (B).

In summary, our data demonstrated that ketamine anaesthesia prevented the increase in CO, which is expected during normovolaemic haemodilution. Under these conditions, the only mechanism allowing maintenance of adequate tissue oxygen delivery is the oxygen extraction reserve. This mechanism allows maintenance of tissue oxygenation to a critical haemoglobin concentration of 3.5–4.0 g dl kg^{-1}. The physiological response to progressive haemodilution we observed was not influenced by the type of synthetic colloid used (gelatin or hydroxyethylstarch). At the regional level, despite an increase in splanchnic blood flow, oxygen availability to the gut may be threatened by weaker tissue extraction capabilities and to the kidneys by decreased blood flow as a result of redistribution of CO to other organs.

Acknowledgement

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References

1. Janvier G, Annat G. Are there limits to haemodilution? *Annales Francaises d'Anesthesie et de Réanimation* 1995; 14: 9–20.
2. Welch GH, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Annals of International Medicine* 1992; **116**: 393–402.
3. Spahn DR, Leone BJ, Reves JG, Pasch T. Cardiovascular and coronary physiology of acute isovolemic hemodilution· a review of nonoxygen-carrying and oxygen-carrying solutions *Anesthesia and Analgesia* 1994; **78**: 1000–1021.
4. Biboulet P, Capdevila X, Benetreau D, Aubas P, D'Athis F, Du Cailar J. Haemodynamic effects of moderate normovolaemic haemodilution in conscious and anaesthetized patients. *British Journal of Anaesthesia* 1996; **76**: 81–84.
5. Lacks H, Pilon RN, Klovekorn WP, Anderson W, Mac Callum JR, O'Connor NE. Acute hemodilution: its effects on hemodynamics and oxygen transport in anesthetized man. *Annals of Surgery* 1974; **180**: 108–109.
6. Vincent JL. Determination of oxygen delivery and consumption vs cardiac index and oxygen extraction ratio. *Critical Care Clinics* 1996; **12**: 995–1006.
7. Fontana JL, Welborn L, Mongan PD, Sturm P, Martin G, Bünger R. Oxygen consumption and cardiovascular function in children during profound intraoperative normovolemic hemodilution. *Anesthesia and Analgesia* 1995; **80**: 219–225.
8. Spahn DR, Zollinger A, Schlumpf RB, Stohr S, Seifert B, Schmid ER, Pasch T. Hemodilution in elderly patients without known cardiac disease. *Anesthesia and Analgesia* 1996; **82**: 681–686.
9. Gisselsson L, Rosberg B, Ericsson M. Myocardial blood flow oxygen uptake and carbon dioxide release of the human heart during hemodilution. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 589–591.
10. Kreimer U, Messmer K. Hemodilution in clinical surgery: State of the art 1996. *World Journal of Surgery* 1996, **20**: 1208–1216.

11. Habler OP, Kleen MS, Podtschaske AH, Hutter JW, Tiede M, Kemming GI, Welte MV, Corso CO, Messmer K. The effect of acute normovolemic hemodilution (ANH) on myocardial contractility in anesthetized dogs. *Anesthesia and Analgesia* 1996; **83**: 451–458.
12. Messmer K, Sunder-Plasmann L, Klövekorn WP, Holper K. Circulatory significance of hemodilution: rheological changes and limitations. *Advances in Microcirculation* 1972; **4**: 1–77.
13. Schou H, Perez de Sa V, Sigurdardottir M, Roscher R, Jonmarker C, Werner O. Circulatory effects of hypoxia, acute normovolemic hemodilution and their combination in anesthetized pigs. *Anesthesiology* 1996; **84**: 1443–1454.
14. Chapler CK, Cain CM. The physiologic reserve in oxygen carrying capacity: studies in experimental hemodilution. *Canadian Journal of Physiology and Pharmacology* 1986; **64**: 7–12.
15. Crystal GJ, Salem MR. Myocardial and systemic hemodynamics during isovolemic hemodilution alone or combined with nitroprusside-induced controlled hypotension. *Anesthesia and Analgesia* 1991; **72**: 227–237.
16. van Woerkens ECSM, Trouwborst A, Duncker DJGM, Koning MMG, Boosma F, Verdouw PD. Catecholamines and regional hemodynamics during isovolemic hemodilution in anesthetized pigs. *Journal of Applied Physiology* 1992; **72**: 760–769.
17. Saddler JM, Horsey PJ. The new generation gelatins. *Anaesthesia* 1987; **42**: 998–1004.
18. Van der Linden P, Schmartz D. Pharmacology of gelatins. In: Baron JF, ed *Plasma Volume Expansion*. Paris: Arnette Blackwell, 1992; 67–74.
19. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitute. *Lancet* 1977; **1**: 467–469.
20. Mishler IV JM. Synthetic plasma volume expanders—their pharmacology, safety and clinical efficacy. *Clinics in Haematology* 1984; **13**: 75–92.
21. Warren BB, Durieux ME. Hydroxyethyl starch. Safe or not? *Anesthesia and Analgesia* 1997; **84**: 206–212
22. Strauss RG, Stansfield C, Henriksen RA, Villhauer PJ. Pentastarch may cause fewer effects on coagulation than hetastarch. *Transfusion* 1988; **28**: 257–260.
23. White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 1982; **56**: 119–136.
24. Van der Linden P, Gilbart E, Engelman D, Schmartz D, Vincent J. Effects of anesthetic agents on systemic critical O_2 delivery. *Journal of Applied Physiology* 1991; **71**: 83–93.
25. Hill RW. Determination of oxygen consumption by use of the paramagnetic oxygen analyzer. *Journal of Applied Physiology* 1972; **33**: 261–263.
26. Samsel RW, Schumacker PT. Determination of the critical O_2 delivery from experimental data: sensitivity to error. *Journal of Applied Physiology* 1988; **64**: 2074–2082.
27. Traber DL, Wilson RD, Priano LL. Differentiation of the cardiovascular effects of CI-581. *Anesthesia and Analgesia* 1968; **47**: 769–787.
28. Chodoff P. Evidence for a central adrenergic action of ketamine. *Anesthesia and Analgesia* 1972; **51**: 247–250.
29. Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *Journal of Applied Physiology* 1977; **42**: 228–234.
30. Rasänen J. Supply-dependent oxygen consumption and mixed venous oxyhemoglobin saturation during isovolemic hemodilution in pigs. *Chest* 1992; **101**: 1121–1124.
31. van Woerkens ECSM, Trouwborst A, van Lanschot JJB. Profound hemodilution: what is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? *Anesthesia and Analgesia* 1992; **75**: 818–821.
32. Crystal GJ, Rooney MW, Ramez Salem M. Regional hemodynamics and oxygen supply during isovolemic hemodilution alone or in combination with adenosine-induced controlled hypotension. *Anesthesia and Analgesia* 1988; **67**: 211–218.
33. Kiel JW, Riedel GL, Shepherd AP. Effects of hemodilution on gastric and intestinal oxygenation. *American Journal of Physiology* 1989; **256**: H171–178.
34. Nöldge GFE, Priebe HJ, Bohle W, Buttler KJ, Geiger K. Effects of acute normovolemic hemodilution on splanchnic oxygenation and on hepatic histology and metabolism in anesthetized pigs. *Anesthesiology* 1991; **7**: 908–918.
35. Audibert G, Donner M, Lefèvre JC, Stolz JF, Laxenaire MC. Rheologic effects of plasma substitutes used for preoperative hemodilution. *Anesthesia and Analgesia* 1994; **78**: 740–745.
36. Van der Linden P, Wathieu M, Gilbart E, Engelman E, Wautrecht JC, Lenaers A, Vincent JL. Cardiovascular effects of moderate normovolaemic haemodilution during enflurane–nitrous oxide anaesthesia in man. *Acta Anaesthesiologica Scandinavica* 1994, **38**: 490–498.
37. Van der Linden P, Gilbart E, Paques P, Simon C, Vincent JL. Influence of hematocrit on tissue O_2 extraction capabilities in anesthetized dogs during acute hemorrhage. *American Journal of Physiology* 1993; **264**: H1942–1947.
38. Jones RM. Clinical comparison of inhalation anesthetic agents. *British Journal of Anaesthesia* 1984; **56**: 57S–69S.
39. Schwartz DA, Horwitz LD. Effects of ketamine on left ventricular performance. *Journal of Pharmacology and Experimental Therapeutics* 1975; **194**: 410–414.
40. Dobson MB. Anaesthesia with ketamine and thiopentone for short surgical procedures. *Anaesthesia* 1978; **33**: 268–270.
41. Traber DL, Wilson RD, Priano LL. A detailed study of the cardiopulmonary responses to ketamine and its blockade by atropine. *Southern Medical Journal* 1970; **63**: 1077–1081.
42. Slogoff S, Allen GW. The role of baroreceptors in the cardiovascular response to ketamine. *Anesthesia and Analgesia* 1974; **53**: 704–707

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Suppression of parasympathetic reflex vasodilatation in the lower lip of the cat by isoflurane, propofol, ketamine and pentobarbital: implications for mechanisms underlying the production of anaesthesia

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Summary

We have compared the effects of isoflurane, propofol, ketamine and pentobarbital on parasympathetic reflex vasodilatation to investigate their involvement in GABA-mediated synaptic inhibition, enhancement of which is thought to underlie the action of many anaesthetic agents. In cats anaesthetized with urethane–α-chloralose, parasympathetic reflex vasodilatation in the ipsilateral lower lip was elicited by electrical stimulation of the central cut end of the lingual nerve. Isoflurane and pentobarbital both produced marked dose-dependent inhibition of this vasodilator response. In contrast, propofol and ketamine had no effect on parasympathetic reflex vasodilatation. Administration of a GABA antagonist (picrotoxin) reversed the inhibition produced by isoflurane (previous results) and pentobarbital (present study). Our results suggest that isoflurane and pentobarbitone inhibit parasympathetic reflex vasodilatation via a GABA-mediated mechanism, but that propofol and ketamine have no such effect. Our results with propofol cast doubt on its presumed mechanism of action as an anaesthetic. (*Br. J. Anaesth.* 1998; **81**: 563–568).

Keywords: anaesthetics volatile, isoflurane, anaesthetics i.v., propofol, anaesthetics i.v., ketamine; hypnotics barbiturate, pentobarbital; parasympathetic nervous system; brain, GABA

The precise mechanism by which many anaesthetic agents exert their action remains unknown, as does their site of action.[1–3] However, there is a considerable body of evidence to suggest that enhancement of GABA-mediated synaptic inhibition may be a common mode of action among anaesthetic agents.[1,4,5] In particular, barbiturates,[6–12] volatile anaesthetics (isoflurane,[1,11,13,14] halothane,[1,13,15] enflurane,[1,13,14] sevoflurane[16]) and propofol have been reported to enhance the action of GABA within the central nervous system.[17–20] Indeed, the main sites at which these anaesthetics act to induce anaesthesia are considered to be GABA receptors. In contrast, ketamine is an anaesthetic which is considered to have little effect on the action of GABA.[6,17,21,22]

We have reported previously that at clinically used concentrations, isoflurane produced marked suppression of parasympathetic reflex vasodilatation in the orofacial area in cats anaesthetized with urethane–α-chloralose.[23] Pretreatment with the GABA receptor antagonist picrotoxin significantly attenuated isoflurane-induced inhibition, suggesting that GABAergic neurones are activated by isoflurane and then inhibit parasympathetic neurones[23] within the central nervous system, possibly by a direct action at the brainstem level. This may suggest that inhalation anaesthetics act on the parasympathetic reflex pathway by a mechanism similar to that by which they induce anaesthesia. However, in our preliminary experiments with propofol, which is considered to exert its action via enhancement of GABA, we detected no inhibitory effect on parasympathetic reflex vasodilatation. These results question whether anaesthetics considered to enhance GABA within the central nervous system inhibit the parasympathetic reflex response also.

In this study, we have compared the effects of pentobarbital, propofol, isoflurane and ketamine on parasympathetic reflex vasodilatation and examined the involvement of GABA receptors in the modulation of this response.

Materials and methods

The studies were reviewed by the Committee on the Ethics of Animal Experiments, Tohoku University School of Medicine, and the study was carried out in accordance with the Guidelines for Animal Experiments issued by Tohoku University School of Medicine, and The Law (No. 105) and Notification (No. 6) of the Japanese Government. We studied 27 adult cats of both sexes, weighing 2.2–3.7 kg, sedated initially with ketamine 30 mg kg^{-1} i.m. and anaesthetized with a mixture of urethane 100 mg kg^{-1} i.v. and α-chloralose 50 mg kg^{-1} i.v., which was used to produce basal anaesthesia unless otherwise noted. In experiments to test the effect of urethane combined with α-chloralose on parasympathetic reflex vasodilatation, propofol 9 mg kg^{-1} h^{-1} was used as the basal anaesthetic. The effects of anaesthetics on parasympathetic reflex vasodilatation were tested 2–3 h after the initial sedation had been produced with ketamine. As the effects of ketamine are short-lasting (30–60 min after i.m. injection), the initial sedative dose should not have affected subsequent responses. Basal anaesthetics were supplemented when neces-

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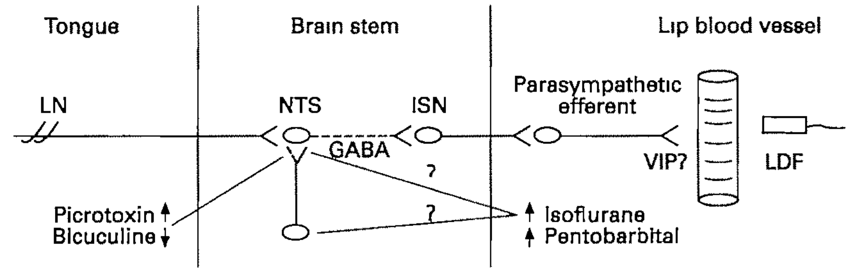

Figure 1 Schematic representation of the putative peripheral and central pathways and mechanisms involved in the action of anaesthetics on parasympathetic reflex vasodilatation. Electrical stimulation was applied to the central cut end of the lingual nerve (LN). The blood flow response of lip blood vessels was measured by a laser Doppler flowmeter (LDF). NTS=Nucleus of the solitary tract. ISN=Inferior salivatory nucleus.

sary throughout the experiment. In the anaesthetized animals, the trachea was intubated, and neuromuscular block was produced by pancuronium (Mioblock, Organon) 0.4 mg kg^{-1} i.v. initially, supplemented with 0.2 mg kg^{-1} h^{-1}. The lungs were ventilated artificially via the tracheal cannula using a mixture of 50% air–50% oxygen. End-tidal concentration of carbon dioxide and inspired and end-tidal concentrations of the inhalation anaesthetics were monitored continuously using an infrared analyser (Capnomac Ultima, Datex Co. Helsinki, Finland). The ventilator was set to maintain end-tidal concentration of carbon dioxide at 4.9 kPa. Systemic arterial pressure and heart rate were recorded directly from a femoral artery catheter connected to a Statham pressure transducer. Ringer's solution was infused continuously at a rate of approximately 8 ml h^{-1}. Rectal temperature was maintained at 37–38°C using a heating pad.

In all experiments, the vagus and sympathetic trunks in the neck were cut bilaterally before stimulation. This avoided involvement of the cervical sympathetics in any reflex effects, and ensured that only non-vagal parasympathetic effects were involved in the study.

To elicit parasympathetic reflex vasodilatation in the lower lip, the central cut end of the lingual nerve was stimulated electrically at a supramaximal intensity (30 V) with pulses of 2 ms duration at a frequency of 10 Hz for 20 s, as described previously.[24] Changes in ipsilateral lower lip blood flow were monitored using a laser Doppler flowmeter (LDF; Advance ALF21R, Tokyo, Japan) as described previously.[25] The probe was placed against the lower lip without exerting pressure on the tissues (fig. 1). LDF values obtained in this way represent blood flow in the superficial vessels in the tissue. Electrical calibration for zero blood flow was performed for all recordings. Several gains were selectable and the maximum output of a given gain level (defined electrically) was taken as 100%. The analogue output of the equipment does not give absolute values, but showed relative changes in blood flow (for technical details and evaluation of the LDF method, see Stern and colleagues[26]). The output from the device was displayed continuously on an eight-channel chart recorder at a speed of 10 mm min^{-1}. Blood flow changes were assessed by measuring the height of the response.

The concentration of isoflurane was determined by analysing inspired and end-tidal samples of respiratory gases obtained from a nylon catheter positioned within the tracheal tube. Propofol was administered continuously as an i.v. infusion, whereas pentobarbital, ketamine, urethane–a-chloralose and picrotoxin were administered i.v. by bolus injection.

Each cat was killed at the end of the experiment by an overdose of sodium pentobarbital (approximately 150 mg).

The criteria for maintenance of an adequate depth of anaesthesia were persistence of miotic pupils and absence of reflex increase in heart rate and arterial pressure during stimulation of the central end of the lingual nerve. If depth of anaesthesia was considered inadequate, additional α-chloralose and urethane (i.e. intermittent doses of 5 and 10 mg kg^{-1} i.v, respectively) were administered. When an adequate depth of anaesthesia was attained, supplementary doses of pancuronium were given approximately every 60 min to maintain immobilization during periods of stimulation.

All numerical data are given as mean (SEM). The significance of changes in vasodilator responses was assessed using analysis of variance (ANOVA) and a contrast test. Differences were considered significant at $P<0.05$. Data were analysed using a Macintosh computer with StatView 4.5 and Super ANOVA.

Results

Figure 2 shows typical examples of the effects of propofol 9 mg kg^{-1} h^{-1} and 1.6% isoflurane on the

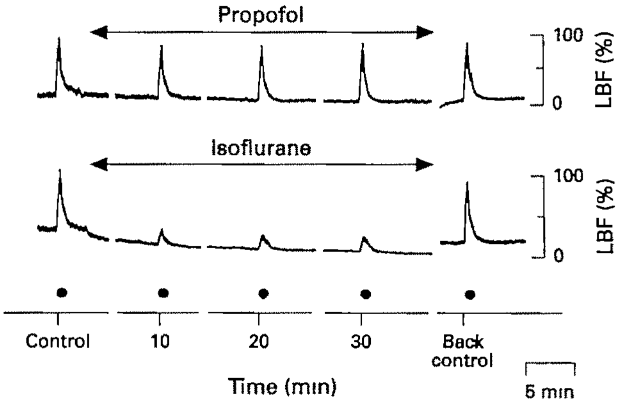

Figure 2 Typical examples of the effects of propofol 9 mg kg^{-1} h^{-1} and 1.6% isoflurane on the increase in lower lip blood flow (LBF) elicited by electrical stimulation of the central cut end of the lingual nerve in vago-sympathectomized cats. The lingual nerve was stimulated where indicated by the filled circles at supramaximal intensity (30 V) with 2 ms pulses at 10 Hz for 20 s. Top, effect of propofol; bottom: effect of isoflurane. The double-headed arrow indicates the period during which each anaesthetic was administered (30 min). "Back control" indicates the response to lingual nerve stimulation 20 min after cessation of administration of anaesthetic.

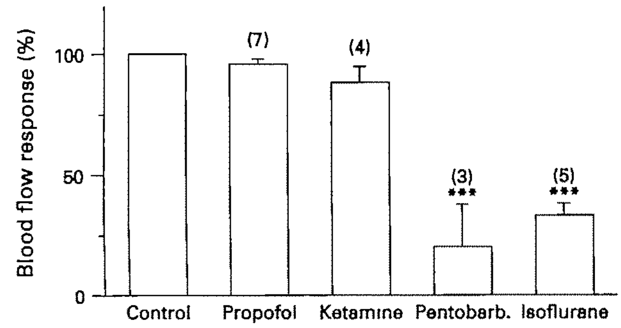

Figure 3 Effects of propofol 9 mg $kg^{-1}h^{-1}$, ketamine 10 mg kg^{-1}, pentobarbital (Pentobarb.) 20 mg kg^{-1} and 1.6% isoflurane on parasympathetic reflex vasodilatation in the lower lip elicited by stimulation of the central cut end of the lingual nerve with a supramaximal intensity (30 V) at 10 Hz (2 ms pulse duration) for 20 s. The vasodilator responses under the various anaesthetics were measured at the following times: propofol, 30 min after the start of infusion; ketamine, 10 min after injection; pentobarbital, 60 min after injection; isoflurane, 30 min after the start of inhalation. The vasodilator response under each anaesthetic is expressed as a percentage of the pretreatment response and is given as mean (SEM). The number of cats used is shown in parentheses. $^{***}P<0.001$ compared with control.

increase in ipsilateral blood flow in the lower lip elicited by electrical stimulation of the central cut end of the lingual nerve. Administration of propofol had little effect on the vasodilator response during the period of study, but isoflurane produced significant inhibition during inhalation, followed by complete recovery within 20 min of cessation of isoflurane.

Figure 3 shows the effects of propofol 9 mg kg^{-1} h^{-1}, ketamine 10 mg kg^{-1}, pentobarbital 20 mg kg^{-1} and 1.6% isoflurane on parasympathetic reflex vasodilatation elicited by stimulation of the central cut end of the lingual nerve. Propofol and ketamine had little or no effect on parasympathetic reflex vasodilatation (propofol –4.0 (1.7)%, n=7, ns; ketamine –11.6 (5.5)%, n=4, ns), but pentobarbital and isoflurane produced marked decreases in this response (pentobarbital –79.3 (17.5)%, n=3, $P<0.001$; isoflurane –66.1 (5.2)%, n=5, $P<0.001$).

Figure 4 shows the time course of the effect of pentobarbital on parasympathetic reflex vasodilatation and the effects of picrotoxin. The reductions produced by pentobarbital at 10, 20, 30 and 40 min after its administration were 84.8 (6.7)% (n=7, $P<0.001$), 79.7 (10.0)% (n=7, $P<0.001$), 78.1 (9.5)% (n=7, $P<0.001$) and 79.3 (17.5)% (n=3, $P<0.001$) of control, respectively. This inhibitory effect was greatly attenuated by picrotoxin; 10 min after administration of picrotoxin, the vasodilator response was significantly greater than that seen at the same time in its absence ($P<0.05$). The vasodilator response after picrotoxin was only 24.1 (8.9) % less than the control response recorded before injection of pentobarbital (n=4, $P<0.05$).

The dose-related effects of propofol and isoflurane are shown in figure 5. In each case, the parasympathetic reflex vasodilator response was measured after 30 min of infusion. Although isoflurane produced dose-dependent inhibition (0.4%, 0.8% and 1.6% isoflurane produced reductions of 12.5 (1.6)% (n=5, ns), 49.7 (8.7)% (n=5, $P<0.001$) and 66.1 (5.2)% (n=5, $P<0.001$), respectively), propofol had little or no effect on parasympathetic reflex vasodilatation at any dose (2.25, 4.5 and 9 mg kg^{-1} h^{-1} produced reductions of 7.0 (1.6)% (n=5, ns), 7.5 (4.0)%, (n=5, ns) and 4.0 (1.7)% (n=7, ns), respectively).

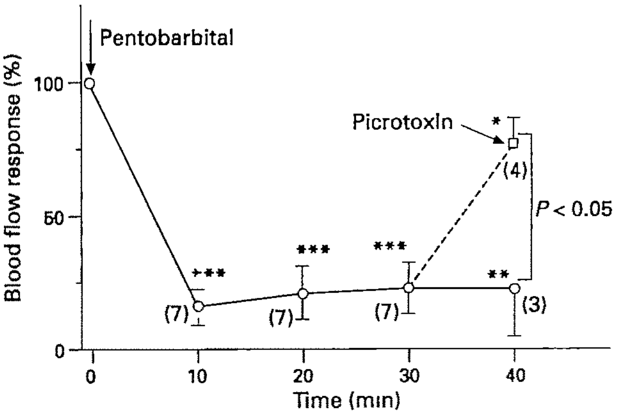

Figure 4 Effect of picrotoxin 2 mg kg^{-1} on pentobarbital-induced suppression of parasympathetic reflex vasodilatation in the lower lip elicited by electrical stimulation of the central cut end of the lingual nerve with a supramaximal intensity (30 V) at 10 Hz (2 ms pulse duration) for 20 s. Drugs were administered where indicated by the arrows. Solid line shows the effect of pentobarbital on parasympathetic reflex vasodilatation, and dashed line shows the effect of picrotoxin on this response. Time (min)=time after administration of pentobarbital. The vasodilator response after administration of pentobarbital or picrotoxin is expressed as a percentage of the response at time 0 and is given as mean (SEM) $^{*}P<0.05$; $^{***}P<0$ 001 *vs* before administration of pentobarbital. $P<0.05$ indicates significant difference between the two data points. The number of cats used is shown in parentheses.

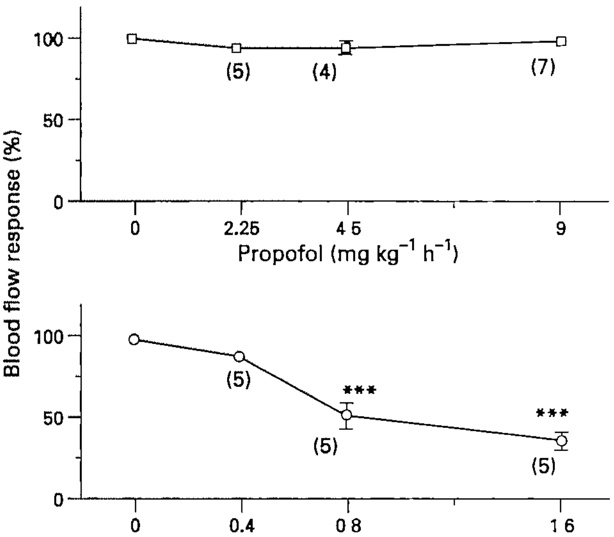

Figure 5 Dose-related effects of propofol 0–9 mg $kg^{-1}h^{-1}$ (top) and 0–1.6% isoflurane (bottom) on parasympathetic reflex vasodilatation in the lower lip elicited by stimulation of the central cut end of the lingual nerve with a supramaximal intensity (30 V) at 10 Hz (2 ms pulse duration) for 20 s Vasodilator responses were measured 30 min after the beginning of infusion or inhalation of anaesthetic. Responses are expressed as percentage of the pretreatment response and each is given as mean (SEM). The number of cats used is shown in parentheses. $^{***}P<0$ 001 *vs* before administration of isoflurane.

Figure 6 shows the time-related effect on parasympathetic reflex vasodilatation of urethane 100 mg kg^{-1} with α-chloralose 50 mg kg^{-1}, which we used to produce basal anaesthesia throughout the experiments. In the experiments illustrated in figure 6, propofol

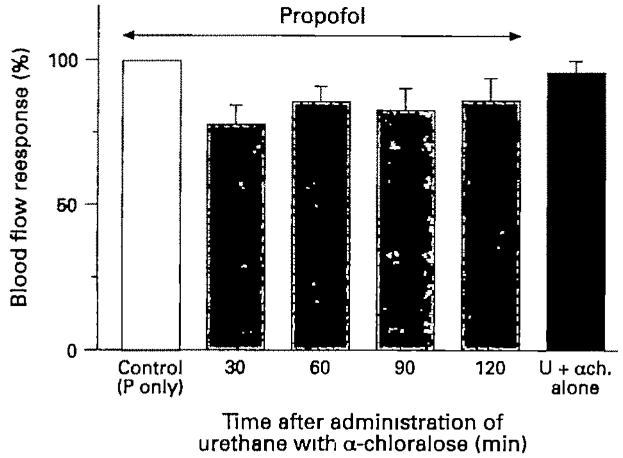

Figure 6 Time-related effects of urethane–α-chloralose (100 and 50 mg kg^{-1}, respectively) with propofol 9 mg kg^{-1} h^{-1} anaesthesia on the increase in lower lip blood flow (LBF) elicited by electrical stimulation of the central cut end of the lingual nerve (30 V, 10 Hz, 2 ms, 20 s) in vago-sympathectomized cats. Vasodilator responses are expressed as a percentage of the control response (evoked in the presence of propofol) and each is given as mean (SEM). The number of cats used was four. Open and shaded columns show, respectively, the increase in lower lip blood flow elicited by lingual nerve stimulation in the absence (control; propofol only) and presence of urethane–α-chloralose. Filled column shows the increase in lower lip blood flow evoked by lingual nerve stimulation 20 min after cessation of propofol infusion (i.e. during urethane–α-chloralose alone).

9 mg kg^{-1} h^{-1} was used to produce basal anaesthesia. There were no significant differences between the control response (or back control) and responses evoked in the 30–120 min after administration of urethane–a-chloralose.

Discussion

We have shown that parasympathetic reflex vasodilatation in the lower lip of the cat was suppressed by both pentobarbital and isoflurane (but not by propofol or ketamine), and that pentobarbital-induced suppression was largely reversed by picrotoxin, a $GABA_A$ antagonist. We have postulated previously on the existence of tonically active GABA-mediated inhibition of this parasympathetic reflex system, on the basis that i.v. administration of a GABA antagonist such as bicuculline elicits a parasympathetically mediated response similar to the reflex response.[27] Furthermore, we have reported recently[23] that inhalation anaesthetics such as isoflurane, sevoflurane and halothane (each at 1 MAC) markedly inhibited parasympathetic reflex vasodilatation in the lower lip and palate that was elicited by electrical stimulation of the central cut end of the lingual nerve in vaso-sympathectomized cats anaesthetized with urethane–α-chloralose, and that prior administration of picrotoxin, a GABA antagonist, reversed this inhibitory effect of isoflurane. These results suggest that inhalation anaesthetics produce inhibition of parasympathetic reflex responses via activation of GABA receptors or increase in GABA, or both (fig. 1). As the inhibitory action of isoflurane was unaffected by decerebration, it is apparently exerted within the brainstem.[23] These results led us to speculate that any agents that enhance the effect of GABA, such as inhalation anaesthetics, would inhibit parasympathetic reflex vasodilatation in the cat.

Our finding that administration of picrotoxin reversed the inhibition of parasympathetic reflex vasodilatation produced by pentobarbital (fig. 4) is in agreement with our previous results using isoflurane.[23] It is well known that the rostal gustatory zone of the nucleus of the solitary tract (NST) of the rat and the caudal visceroceptive NST contain both GABA and the principle enzyme involved in the degradation of GABA, GABA transaminase.[28] Further, the preganglionic parasympathetic cell bodies of the superior and inferior salivatory nuclei receive direct projection from the NST, in addition to one from the parabrachial nucleus.[29–31] Our data are consistent with the idea that both isoflurane and pentobarbital activate GABA receptors (and/or increase GABA release) within the NST, and that this leads to inhibition of parasympathetic reflex vasodilatation (fig. 1). However, at present this idea is speculative.

Ketamine is thought to inhibit *N*-methyl-D-aspartate (NMDA) receptors and have little effect on GABA receptors within the central nervous system.[6 17 21 22] Our data (fig. 3) showed that administration of ketamine had no effect on parasympathetic reflex vasodilatation, suggesting that NMDA has no influence on this type of reflex vasodilatation.

Propofol has been used widely in clinical practice, and also in experimental studies both *in vivo*[17 19] and *in vitro*.[18–20] It has been reported to enhance the action of GABA within the central nervous system, for example in the cerebral cortex,[18 19] hippocampus[20] and spinal dorsal horn.[17] However, no inhibitory effect of propofol on parasympathetic reflex vasodilator response was observed in our cats anaesthetized with urethane–α-chloralose (fig. 2). These results question whether GABA-enhancing anaesthetics necessarily produce inhibition of parasympathetic reflex vasodilatation. Nevertheless, except in the case of propofol, there seemed to be a close relationship between supposed GABA-enhancing effect and inhibition of parasympathetic reflex vasodilatation. Interestingly, there is evidence of differential effects among anaesthetics, in that propofol has been reported to bind to GABA receptors other than those affected by pentobarbital and isoflurane.[18] There are at least two explanations for the inability of propofol to inhibit parasympathetic reflex vasodilatation: (i) propofol has no ability to enhance the action of GABA within the brainstem, even though it has such an ability in other parts of the CNS (see above) or (ii) propofol cannot produce a further reduction in the parasympathetic reflex vasodilator response recorded under basal urethane–α-chloralose anaesthesia because urethane–α-chloralose had already inhibited the relevant GABA receptors. The first possibility seems unlikely as it requires propofol to enhance the action of GABA at several sites within the brain and spinal cord,[17–20] but not within the brainstem pathway mediating parasympathetic reflex vasodilatation. However, we cannot completely exclude this possibility. The second possibility (that urethane–α-chloralose strongly inhibits the relevant GABA receptors) seems unlikely because urethane has minimal effects on circulatory dynamics, and α-chloralose has comparatively few depressant effects on central nervous structures.[32 33] Moreover, our experiments showed that urethane–α-chloralose had no effect on parasympathetic reflex vasodilatation when propofol was used as the basal anaesthetic (fig. 6).

Propofol has been reported to decrease sympathetic activity more than parasympathetic activity, and to produce bradyarrhythmia, including asystole.[34–38] Our findings that propofol had no effect on reflex activation of the parasympathetic supply to blood vessels is consistent with the idea that parasympathetic activity as a whole is better preserved under propofol. If so, preservation of efferent vagal actions on the heart could help explain the bradyarrhythmia seen with propofol. However, this idea is speculative.

In summary, the results of this and previous studies have demonstrated that anaesthetics such as pentobarbital and isoflurane exert an inhibitory effect on parasympathetic reflex vasodilatation in the lower lip of the cat via activation of GABA receptors, or increased release of GABA, or both, while propofol and ketamine have no such effects. Our results with pentobarbital, isoflurane and ketamine are consistent with the current idea that these agents exert their anaesthetic actions by enhancing the effects of GABA (pentobarbital and isoflurane) or by inhibiting NMDA receptors (ketamine). The lack of effect of propofol in this study casts doubt on the idea that its anaesthetic action is exerted by enhancement of the actions of GABA. However, this requires further study.

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References

1. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature (London)* 1994; **367**: 607–614.
2. Matthews RA. Low-fat theory of anesthesia. *Science* 1992; **255**: 156–157.
3. Franks NP, Lieb WR. Neurone membranes: anaesthetics on the mind. *Nature (London)* 1987; **328**: 113–114.
4. Nicoll RA. The effects of anaesthetics on synaptic excitation and inhibition in the olfactory bulb. *Journal of Physiology (London)* 1972; **223**: 803–814.
5. Tanelian DL, Kosek P, Mody I, MacIver MB. The role of the $GABA_A$ receptor/chloride channel complex in anesthesia. *Anesthesiology* 1993; **78**: 757–776.
6. Olson JJ, Friedman R, Orr K, Delaney T, Oldfield EH. Cerebral radioprotection by pentobarbital: dose–response characteristics and association with GABA agonist activity. *Journal of Neurosurgery* 1990; **72**: 749–758.
7. McGaraughty S, Reinis S, Tsoukatos J. Investigating the role of anaesthetics on the rostral ventromedial medulla: implications for a GABAergic link between ON and OFF cells. *Neuroscience Letters* 1993; **149**: 119–122.
8. Lin LH, Wang LH. Region-specific changes in $GABA_A$ receptor delta subunit mRNA level by tolerance to and withdrawal from pentobarbital. *Neuroscience Letters* 1996; **202**: 149–152.
9. Okamoto T, Kurahashi K, Tsubomura T, Fujiwara M. Effects of barbiturates on the inhibitory action of GABA on excitatory response of the stomach to stimulation of vagal afferent fibers in cat. *Life Sciences* 1987; **41**: 405–411.
10. Sanna E, Garau F, Harris RA. Novel properties of homomeric beta 1 gamma-aminobutyric acid type A receptors: actions of the anesthetics propofol and pentobarbital. *Molecular Pharmacology* 1995; **47**: 213–217.
11. Harris BD, Wong G, Moody EJ, Skolnick P. Different subunit requirements for volatile and nonvolatile anesthetics at gamma-aminobutyric acid type A receptors. *Molecular Pharmacology* 1995; **47**: 363–367.
12. Rho JM, Donevan SD, Rogawski MA. Direct activation of $GABA_A$ receptors by barbiturates in cultured rat hippocampal neurones. *Journal of Physiology (London)* 1996; **497**: 509–522.
13. Jones MV, Brooks PA, Harrison NL. Enhancement of gamma-aminobutyric acid-activated Cl^- currents in cultured rat hippocampal neurones by three volatile anaesthetics. *Journal of Physiology (London)* 1992; **449**: 279–293.
14. Nakahiro M, Yeh JZ, Brunner E, Narahashi T. General anesthetics modulate GABA receptor channel complex in rat dorsal root ganglion neurons. *FASEB Journal* 1989; **3**. 1850–1854.
15. Cheng SC, Brunner EA. Effects of anesthetic agents on synaptosomal GABA disposal. *Anesthesiology* 1981; **55**. 34–40.
16. Wu J, Harata N, Akaike N. Potentiation by sevoflurane of the gamma-aminobutyric acid-induced chloride current in acutely dissociated CA1 pyramidal neurones from rat hippocampus. *British Journal of Pharmacology* 1996; **119**: 1013–1021.
17. Uchida H, Kishikawa K, Collins JG. Effect of propofol on spinal dorsal horn neurons. Comparison with lack of ketamine effects. *Anesthesiology* 1995; **83**: 1312–1322.
18. Hales TG, Lambert JJ. The actions of propofol on inhibitory amino acid receptors of bovine adrenomedullary chromaffin cells and rodent central neurones. *British Journal of Pharmacology* 1991; **104**: 619–628.
19. Peduto VA, Concas A, Santoro G, Biggio G, Gessa GL. Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in the rat brain *Anesthesiology* 1991; **75**: 1000–1009.
20. Hara M, Kai Y, Ikemoto Y. Propofol activates $GABA_A$ receptor–chloride ionophore complex in dissociated hippocampal pyramidal neurons of the rat. *Anesthesiology* 1993; **79**: 781–788.
21. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *British Journal of Pharmacology* 1983; **79**: 565–575.
22. Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. *British Journal of Anaesthesia* 1996; **77**: 441–444.
23. Izumi H, Ito Y, Sato M, Karita K, Iwatsuku N Effect of inhalation anesthetics on the parasympathetic reflex vasodilation in the lower lip and palate of the cat. *American Journal of Physiology* 1997; **273**: R168–174.
24. Izumi H, Karita K. The parasympathetic vasodilator fibers in the trigeminal portion of the distal lingual nerve in the cat tongue. *American Journal of Physiology* 1994; **266**. R1517–1522.
25. Izumi H, Karita K. Somatosensory stimulation causes autonomic vasodilatation in cat lip. *Journal of Physiology (London)* 1992; **450**: 191–202.
26. Stern MD, Lappe DL, Bowen PD, Chimosky JE, Holloway GA Jr, Keiser HR, Bowman RL. Continuous measurement of tissue blood flow by laser-Doppler spectroscopy. *American Journal of Physiology* 1977, **232**: H441–448.
27. Izumi H, Takahashi H, Karita K. Pentylenetetrazole-induced parasympathetic blood flow increase in the lower lip of the cat. *European Journal of Pharmacology* 1995; **273**: 299–302.
28. Lasiter PS, Kachele DL. Organization of GABA and GABA-transaminase containing neurons in the gustatory zone of the nucleus of the solitary tract. *Brain Research Bulletin* 1988; **21**: 623–636.
29. Contreras RJ, Gomez MM, Norgren R. Central origins of cranial nerve parasympathetic neurons in the rat. *Journal of Comparative Neurology* 1980; **190**: 373–394.
30. Hanamori T, Smith DV. Gustatory innervation in the rabbit: central distribution of sensory and motor components of the chorda tympani, glossopharyngeal, and superior laryngeal nerves. *Journal of Comparative Neurology* 1989; **282**: 1–14
31. Ricardo JA, Koh ET. Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. *Brain Research* 1978; **153**. 1–26.
32. Farber NE, Samso E, Kampine JP, Schmeling WT. The effects of halothane on cardiovascular responses in the neuraxis of cats. *Anesthesiology* 1995; **82**: 153–165.
33. Saito R, Graf R, Hubel K, Taguchi J, Rosner G, Fujita T, Heiss WD. Halothane, but not alpha-chloralose, blocks potassium-evoked cortical spreading depression in cats. *Brain Research* 1995; **699**: 109–115.
34. Krassioukov AV, Gelb AW, Weaver LC. Action of propofol on central sympathetic mechanisms controlling blood pressure. *Canadian Journal of Anaesthesia* 1993; **40**: 761–769.

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Volatile anaesthetics have differential effects on recombinant m1 and m3 muscarinic acetylcholine receptor function†

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Summary

Muscarinic acetylcholine signalling plays major roles in regulation of consciousness, cognitive functioning, pain perception and circulatory homeostasis. Halothane has been shown to inhibit m1 muscarinic signalling. However, no comparative data are available for desflurane, sevoflurane or isoflurane, nor have the anaesthetic effects on the m3 subtype (which is also prominent in the brain) been studied. Therefore, we have investigated the effects of these compounds on isolated m1 and m3 muscarinic receptor function. Defolliculated *Xenopus* oocytes expressing recombinant m1 or m3 muscarinic or (for comparison) AT_{1A} angiotensin II receptors were voltage clamped, and Ca^{2+}-activated Cl^- currents ($I_{Cl(Ca)}$) induced by acetyl-β-methylcholine (Mch) or angiotensin II were measured in the presence of clinically relevant concentrations of halothane, sevoflurane, desflurane or isoflurane. To determine the site of action of the volatile anaesthetics we compared anaesthetic effects on m1, m3 and AT_{1A} receptor function and studied the effects of volatile anaesthetics on signalling induced by intracellular injection of the second messenger IP_3. Desflurane had a biphasic effect on m1 signalling, enhancing at a concentration of 0.46 mmol litre^{-1} but depressing at 0.92 mmol litre^{-1}. A similar, although not significant, trend was observed with m3 signalling. Isoflurane had no effect on m1 signalling, but profoundly inhibited m3 signalling. Sevoflurane depressed the function of m1 and m3 signalling in a dose-dependent manner. Halothane, similar to its known effect on m1 signalling, dose-dependently depressed m3 function. $I_{Cl(Ca)}$ induced by intracellular injections of IP_3 were unaffected by all four anaesthetics. Similarly, none of the anaesthetics tested affected AT_{1A} signalling. Absence of interference with AT_{1A} signalling and intracellular pathways suggest that the effects of anaesthetics on muscarinic signalling most likely result from interactions with the m1 or m3 receptor molecule. Multiple interaction sites with different affinities may explain the biphasic response to desflurane. Anaesthetic-specific effects on closely related receptor subtypes suggest defined sites of action for volatile anaesthetics on the receptor protein. (*Br. J. Anaesth.* 1998; **81**: 569–577).

Keywords: theories of anaesthetic action, molecular; anaesthetics volatile; receptors, muscarinic

In addition to the well known actions in circulatory and respiratory regulation,[1 2] muscarinic acetylcholine signalling plays an important role in the central nervous system (CNS). Level of consciousness is modulated significantly by brainstem muscarinic signalling.[3] Cholinergic antagonists affect memory and learning abilities through actions on the basal forebrain, cortex and hippocampus.[4 5] Spinal muscarinic receptors mediate antinociception, predominantly in the substantia gelatinosa of the dorsal horn, and also affect motor neurone areas.[6 7]

Anaesthetics cause CNS depression and alter bronchial tone and heart rate, effects which may be mediated in part by interactions with muscarinic signalling.[8 9] Various anaesthetics are known to alter ligand binding to muscarinic receptors. Ether,[10] halothane,[11] chloroform, enflurane and isoflurane[12] were shown to increase muscarinic antagonist binding. However, these initial reports investigated mixed receptor populations and did not study receptor activation. More refined methods of investigating anaesthetic mechanisms became available when the members of the muscarinic receptor subfamily were cloned. Hence the influence of anaesthetics on the function of individual receptor subtypes can now be studied. Recently, we reported that halothane[13] and ketamine[14] inhibited m1 muscarinic signalling.

This study was designed to extend the initial findings with halothane. First, we wished to investigate if the effect of halothane on muscarinic signalling was subtype-specific. Therefore, we studied anaesthetic actions on the m3 muscarinic receptor, which is also expressed widely in brain.[15 16] Second, we wished to investigate if the effects of halothane could be extrapolated to other volatile anaesthetics. Thus we studied the muscarinic inhibitory effects of sevoflurane, isoflurane and desflurane. The comparison between isoflurane and desflurane was of specific interest, as these anaesthetics are closely related structurally: desflurane differs from isoflurane only in the substitution of fluorine for chlorine on the α-ethyl carbon. However, in contrast with isoflurane, desflurane has been noted to induce a relative sympathetic activation, resulting in significantly increased heart rate and mean arterial pressure compared with isoflurane.[17–19]

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We hypothesized that this effect might result in part from muscarinic inhibition, and that, despite their structural similarities, these anaesthetics might show divergent effects on muscarinic receptor function.

Therefore, we have determined the action of desflurane, isoflurane and sevoflurane on m1 and m3 muscarinic and, as a comparison, on angiotensin II receptor function. In addition, the effects of halothane on m3 signalling were investigated. Specifically, we investigated if the anaesthetics, at clinically comparable concentrations, influenced m1 and m3 muscarinic signalling, and where in the signalling pathway their effects were localized.

Materials and methods

XENOPUS OOCYTES

The study was approved by the Animal Research Committee of the University of Virginia. Adult female *Xenopus laevis* frogs were obtained from Xenopus I (Ann Arbor, MI, USA) and housed in an established frog colony. To obtain oocytes, frogs were anaesthetized with 1% tricaine (3-aminobenzoic acid ethyl ester) until unresponsive, and operated on ice. Oocytes were harvested via a 5-mm incision in the lower lateral abdominal wall and placed immediately in modified Barth's solution containing (mmol litre^{-1}): NaCl 88, KCl 1, $NaHCO_3$ 2.4, $CaCl_2$ 0.41, $MgSO_4$ 0.82, $Ca(NO_3)_2$ 0.3, gentamicin 0.1, HEPES 15, pH adjusted to 7.6. Frogs were returned to the main tank after recovering for 2 days in isolation. Oocytes (Dumont's stages V and VI) were defolliculated by gentle shaking for 2 h in a solution of 1 mg ml^{-1} collagenase type Ia in calcium-free OR2 solution, containing (mmol litre^{-1}): NaCl 82.5, KCl 2, $MgCl_2$ 1, HEPES 5, pH adjusted to 7.5, and were afterwards incubated in modified Barth's solution at 18°C.

RECEPTOR EXPRESSION

The rat m1 and m3 muscarinic acetylcholine receptors were a gift from T. I. Bonner (National Institutes of Mental Health, Bethesda, MD, USA). Its complementary DNA (cDNA) consists of a 2.8-kilobasepair (kpb) fragment in a commercial vector (pGEM1; Promega, Madison, WI, USA). The construct for m1 expression was linearized by digestion with the nuclease *Hind*III, and complementary RNA (cRNA) was transcribed *in vitro* using the bacteriophage RNA polymerase T7. A capping analogue (^{7m}GpppG) was included in the reaction to generate capped transcripts, as these are translated more efficiently in the oocyte. The resulting cRNA was quantified by spectroscopy and diluted in water to a concentration of 0.1 mg ml^{-1}. Oocytes were each injected with 5 ng of cRNA using an automated microinjector (Nanoject; Drummond Scientific, Broomall, PA, USA). Adequacy of injection was confirmed by noting the slight increase in cell size during injection. m3 muscarinic cDNA was subcloned in the pCMV vector. cDNA 10 ng in H_2O 9.5 nl was injected directly into the germinal vesicle (nucleus) of the oocyte. This technique bypasses *in vitro* cRNA preparation and therefore yields faster and more convenient, although less reliable, expression.

A 1.2-kbp cDNA in the CDM8 vector (Invitrogen, San Diego, CA, USA), encoding the rat AT_{1A} angiotensin II receptor, was obtained from Dr. K. R. Lynch (University of Virginia, Charlottesville, VA, USA). The construct was linearized with the nuclease *Xho*I and transcribed *in vitro* by T7 RNA polymerase in the presence of a capping analogue. Oocytes were injected as described above. All injected cells were cultured for 72 h at 18°C in modified Barth's solution before study.

ELECTROPHYSIOLOGY

m1, m3 or AT_{1A} receptor activation in oocytes leads to G protein-induced phospholipase C activity and release of inositoltrisphosphate (IP_3) from phosphoinositolbisphosphate (fig. 1A). IP_3 then binds to its specific receptor on intracellular Ca^{2+} stores to release Ca^{2+}, which in turn opens an endogenous Ca^{2+}-activated Cl^- channel. The resulting current can be measured by voltage clamp, and this Ca^{2+}-activated Cl^- current ($I_{Cl(Ca)}$), integrated and expressed as micro coulombs (μC), is a measure of intracellular Ca^{2+} release.[20–23] The upward deflection during agonist application at times observed in the traces is a slight motion artefact. All experiments were performed at room temperature (approximately 22°C).

Microelectrodes were pulled in one stage from capillary glass (BBL with fibre; World Precision Instruments, Sarasota, FL, USA) on a micropipette puller (model 700C; David Kopf Instruments, Tujunga, CA, USA). Tips were broken to a diameter of approximately 10 μm, providing a resistance of 1–3 MΩ, and filled with KCl 3 mol litre^{-1}. A single oocyte was placed in a perfusable bath containing 3 ml of Tyrode's solution containing (mmol litre^{-1}): NaCl 150, KCl 5, $MgCl_2$ 1, $CaCl_2$ 2, glucose 10, HEPES 10, pH adjusted to 7.4 with NaOH. Two microelectrodes were inserted into the oocyte, and a holding potential of −70 mV was applied to the membrane. The voltage clamp amplifier (OC725A; Warner Corporation, New Haven, CT, USA) was connected to a data acquisition and analysis system running on an IBM-compatible personal computer. The acquisition system consisted of a DAS-8 A/D conversion board (Keithly-Metrabyte, Taunton, MA) and analysis was performed with OoClamp software.[24] Occasional cells that did not show a stable holding current of less than 1 μA during a 1-min equilibration period were excluded from analysis.

Membrane current was sampled at 125 Hz and recorded for 5 s before and 55 s after application of the agonist (acetyl-β-methylcholine (Mch) or angiotensin II (AT) delivered at appropriate EC_{50} values: Mch 10^{-7} mol litre^{-1} for m1 receptors[13], Mch 10^{-6} mol litre^{-1} for m3 receptors; AT 10^{-7} mol litre^{-1} for AT_{1A} receptors). Agonists were delivered in 30-μl aliquots over 1–2 s using a micropipettor positioned approximately 1 mm from the oocyte. Responses were quantified by integrating the current trace by quadrature and are reported as μC as this reflects intracellular Ca^{2+}-release better than peak current.[25] Any motion artefact on agonist delivery was excluded from analysis. Each oocyte received a single agonist application only.

IP_3 AND HEPARIN MICROINJECTION

To evaluate the influence of volatile anaesthetics on the second messenger system, we injected IP_3 or heparin into the oocyte. Heparin inhibits the IP_3 receptor on intracellular Ca^{2+} stores, thereby inhibiting Ca^{2+} release induced by IP_3-signalling receptors. Heparin injections were performed 30 min before voltage clamping; heparin 120 ng (2 ng nl^{-1}) was microinjected using the same nanoinjector mentioned above. IP_3, when injected into the cell, induces an $I_{Cl(Ca)}$ similar to that observed after receptor activation in the oocyte. IP_3-induced $I_{Cl(Ca)}$ was evoked by injecting 50 nl of IP_3 2 mmol $litre^{-1}$ in water into the oocyte. Each oocyte was injected only once with IP_3; therefore, any kinetic effects observed were not caused by time-dependent effects or run-down after multiple injections. Control injections with water as vehicle were performed to assure a specific action of IP_3.

STATISTICAL ANALYSIS

Results are reported as mean (SEM). As variability between batches of oocytes is common, responses were at times normalized to same-day controls for each batch. Differences between treatment groups were analysed using ANOVA and Student's unpaired *t* test, appropriately corrected for multiple comparisons (Bonferroni). $P<0.05$ was considered significant. Concentration–response curves were fit to the following logistic function, derived from the Hill equation:

$$y = y_{min} + \left(y_{max} - y_{min}\right)\left(1 - \frac{x^n}{x_{50}^n + x^n}\right)$$

where y_{max} and y_{min}=maximum and minimum response obtained, respectively, n=the Hill coefficient, and x_{50}=concentration at which the half-maximal response occurs (EC_{50} for agonist, IC_{50} for anaesthetics). In figure 1D, curve fitting was performed on averaged raw data. In the other graphs, because of variability of oocyte batches from different frogs, data were normalized to the same day control value and then the fitting was performed on the averaged normalized values. All fitting values are given in table 1 and fits were used only if r^2 was greater than 0.95.

MATERIALS

Molecular biology reagents were obtained from Promega (Madison, WI, USA) and other chemicals were obtained from Sigma (St Louis, MO, USA). Volatile anaesthetics (desflurane and isoflurane from Ohmeda Pharmaceutical Products Division, Liberty Corner, NJ, USA, sevoflurane from Abbott Laboratories, North Chicago, IL, USA and halothane from Halocarbon Laboratories, River Edge, NJ, USA) were delivered using agent-specific vaporizers (carrier gas:air at 500 ml min^{-1}) and equilibrated in Tyrode's solution by bubbling for at least 10 min. Oocytes were exposed to anaesthetics for approximately 5 min before testing. Bath concentrations of anaesthetics were verified by gas chromatography (Aerograph 940, Varian Analytical Instruments, Walnut Creek, CA, USA) using saline–gas partition coefficients ($P_{sol/gas}$) at 22°C for isoflurane (1.08), sevoflurane (0.52), halothane (1.20) and desflurane (0.45) (estimations for desflurane and sevoflurane were based on the observation that $P_{sol/gas}$ is approximately twice as great at 22°C as at 37°C).[26-28]

Results

FUNCTIONAL EXPRESSION OF MUSCARINIC AND ANGIOTENSIN RECEPTORS IN *XENOPUS* OOCYTES

Control oocytes were unresponsive to Mch 10^{-7} mol $litre^{-1}$ or AT 10^{-6} mol $litre^{-1}$ (data not shown). Oocytes

Table 1 Curve fitting variables (Hill equation) for Mch concentration–response relationships in *Xenopus* oocytes expressing recombinant m1 or m3 muscarinic acetylcholine receptors and inhibition concentration relationship for isoflurane, sevoflurane and halothane on m1 or m3 muscarinic receptor signalling values. Values are given as mean (SEM).

	EC_{50} (mol $litre^{-1}$)	Hill coefficient	Emax (µC)	r^2
Concentration–response relationship				
muscarinic m1 receptor	$1.3\ (0.15) \times 10^{-7}$	0.83 (0.07)	8.77 (0.14)	0.99
muscarinic m3 receptor	$1.02\ (0.58) \times 10^{-6}$	0.75 (0.27)	9.95 (0.88)	0.96

	EC_{50} (mol $litre^{-1}$)	Hill coefficient	Emax (%)	r^2
Concentration–inhibition relationship				
m3 muscarinic receptor and isoflurane	0.45 (0.06)	1.92 (0.43)	99.12 (6.31)	0.98
m1 muscarinic receptor and sevoflurane	0.32 (0.01)	3.18 (0.32)	97.11 (2.25)	0.99
m3 muscarinic receptor and sevoflurane	0.75 (0.05)	7.25 (3.8)	103.7 (7.56)	0.96
m3 muscarinic receptor and halothane	0.88 (0.02)	5.4 (0.66)	98.61 (2.79)	0.99

injected with mRNA encoding the m1 or AT_{1A} receptor or cDNA encoding m3 muscarinic acetylcholine receptor, respectively, responded with a transient inward current in a concentration-dependent manner (fig. 1B, C, D–fitting values in table 1). Agonist concentrations were chosen to reflect approximate EC_{50} values, as determined in fig. 1D. Currents developed within several seconds after agonist application, and returned to baseline after approximately 30 s. Average response sizes were 3.4 (0.8) μC for the m1 receptor, 5.0 (1.2) μC for the m3 receptor and 1.6 (0.6) μC for the AT_{1A} receptor. These findings are similar to those reported in our previous studies, where we showed that these currents were $I_{Cl(Ca)}$.[13 14]

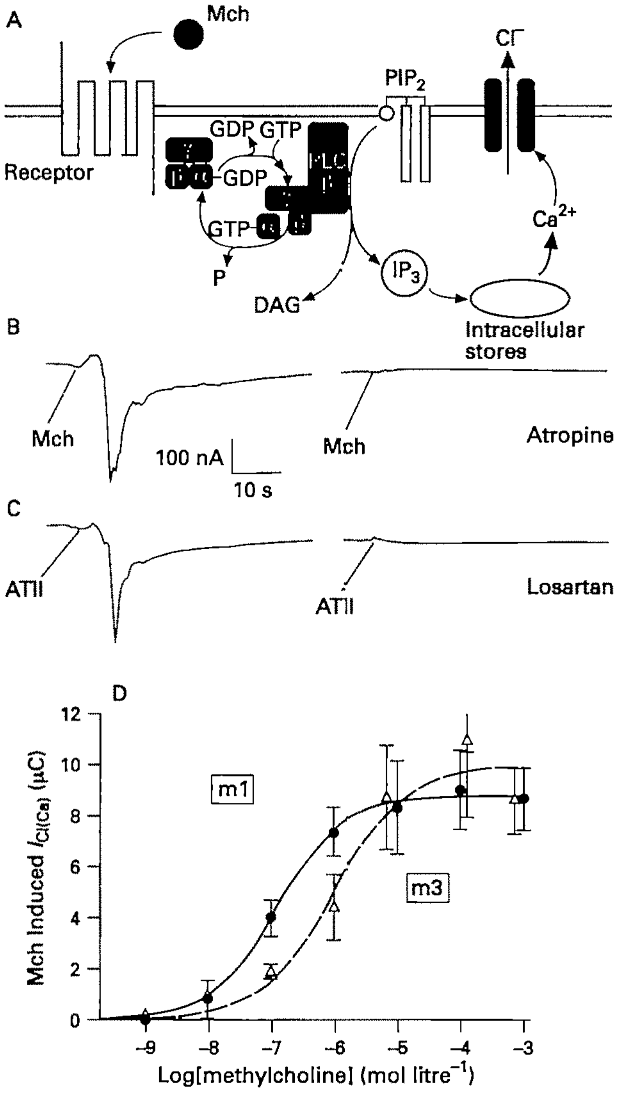

Figure 1 Muscarinic and angiotensin signalling in *Xenopus laevis* oocytes. A: Signalling pathway linking activation of the muscarinic receptor to chloride (Cl⁻) channel opening. The double line represents the cell membrane. The agonist acetyl-β-methylcholine (Mch) binds to a G protein-coupled receptor, which in turn activates phospholipase C (PLC). PLC releases inositoltrisphosphate (IP_3) from cell membrane-bound phosphatidylinositolbisphosphate (PIP_2). Calcium (Ca^{2+}) is released from IP_3-sensitive intracellular stores and activates a Ca^{2+}-dependent Cl⁻channel in the cell membrane. Angiotensin receptors signal over the same pathway. B: Left: Example of inward Ca^{2+}-activated Cl⁻ current ($I_{Cl(Ca)}$) induced by acetyl-β-methylcholine (Mch) 10^{-7} mol litre^{-1} in an oocyte expressing m1 muscarinic rectors. The current is integrated and expressed as charge movement (1.9 μC). Right: The response to Mch can be blocked completely by the antagonist atropine (1 μmol litre^{-1}). Similar observations were obtained with m3 receptors and their specific antagonist 4-DAMP (100 nmol litre^{-1}; data not shown). C: Left: Example of inward Ca^{2+}-activated Cl⁻ current ($I_{Cl(Ca)}$) induced by angiotensin II (ATII) 10^{-7} mol litre^{-1} in an oocyte expressing AT_{1A} receptors. Charge movement is 1.7 μC. Right: The response can be blocked completely by the angiotensin II receptor antagonist losartan (10 μmol litre^{-1}). D. Concentration–response relationship for m1 and m3 muscarinic receptors. Fitting values using the Hill equation are given in table 1.

To ensure that the responses were mediated by specific receptors, we attempted to inhibit them with antagonists. Atropine 1 μmol litre^{-1} completely inhibited responses to Mch in oocytes expressing m1 and m3 receptors (fig. 1B), and the m3-selective antagonist 4-DAMP 100 nmol litre^{-1} inhibited responses of m3 receptors (data not shown). Similarly, the non-peptide angiotensin receptor antagonist losartan 10 μmol litre^{-1} inhibited AT signalling in cells expressing AT_{1A} receptors (fig. 1C).

DESFLURANE AFFECT M1 AND M3 MUSCARINIC SIGNALLING IN A CONCENTRATION-DEPENDENT BIPHASIC MANNER

We then tested the ability of desflurane at various concentrations to influence $I_{Cl(Ca)}$ induced by appropriate Mch concentrations in oocytes expressing m1 (fig. 2A) or m3 receptors. Signalling of m1 receptors was enhanced significantly when desflurane 0.46 mmol litre^{-1} was present in the bath: responses were 71 (28) % greater than control ($P<0.001$, *t* test). Desflurane, at a concentration of 0.70 mmol litre^{-1}, induced no significant change in response (decrease of 12 (17) %; $P=0.47$, *t* test) compared with control. At higher concentrations, desflurane inhibited muscarinic signalling: desflurane 0.92 and 1.66 mmol litre^{-1} reduced responses by 43 (11) % ($P=0.003$, *t* test) and 75 (5) % ($P<0.001$, *t* test), respectively (fig. 2B). Similar results were obtained for m3 signalling (fig. 2C). Thus desflurane had a biphasic, concentration-dependent effect on muscarinic receptor function.

ISOFLURANE DID NOT AFFECT M1, BUT INHIBITED M3 MUSCARINIC SIGNALLING

In contrast with desflurane, isoflurane had no effect on Mch-induced m1 muscarinic signalling (fig. 3A). At very high concentrations (0.75–0.96 mmol litre^{-1}) an inhibitory trend was noted (fig. 3B). However, these effects were not statistically significant. The effects of isoflurane on m1 signalling were therefore different from those of desflurane, especially when the actions of the two compounds were compared at MAC-equivalent concentrations. In contrast with its lack of effect on m1 signalling, isoflurane inhibited m3 signalling (IC_{50} 0.45 mmol litre^{-1}) (fig. 3C).

SEVOFLURANE AND HALOTHANE INHIBITED M1 AND M3 SIGNALLING

Sevoflurane and halothane inhibited m1 and m3 muscarinic signalling. We have reported previously that halothane inhibits m1 signalling with an IC_{50} of 0.3 mmol litre^{-1}.[13] In this study, we found that it inhibited m3 signalling with an IC_{50} of 0.88 mmol litre^{-1} (fig. 4C). Sevoflurane inhibited m1 and m3 signalling in a similar manner (IC_{50} 0.32 mmol litre^{-1} for m1 muscarinic inhibition (fig. 4A) and 0.75 mmol litre^{-1} for m3 muscarinic signalling (fig. 4B)). Thus,

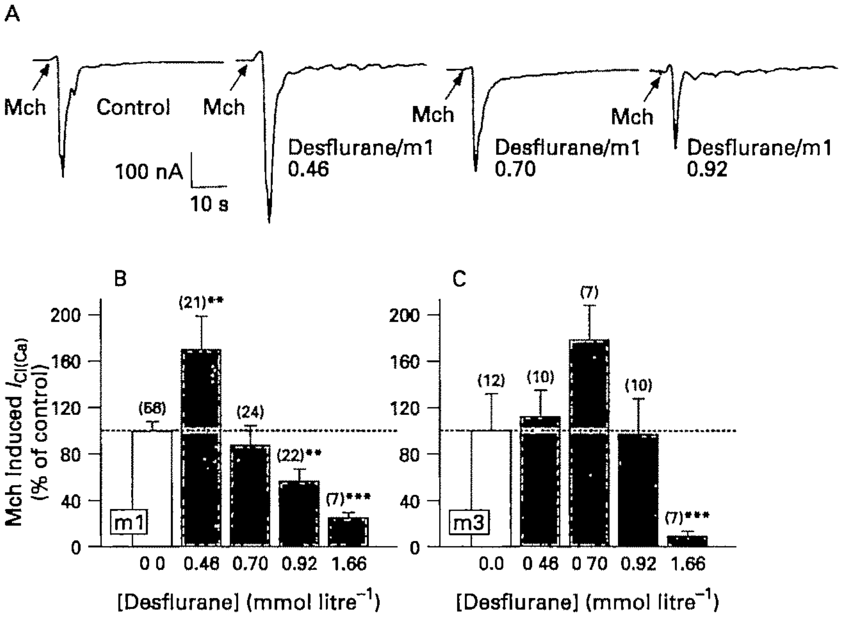

Figure 2 Influence of desflurane on m1 and m3 muscarinic signalling. A: $I_{Cl(Ca)}$ induced by Mch 10^{-7} mol litre^{-1} in oocytes expressing m1 muscarinic receptors at various concentrations of desflurane (desflurane 0 mmol litre^{-1} (1.5 μC), 0.46 mmol litre^{-1} (2.2 μC), 0.70 mmol litre^{-1} (1.4 μC) and 0.92 mmol litre^{-1} (0.7 μC)). B: Desflurane has a biphasic effect on Mch-induced $I_{Cl(Ca)}$ in oocytes expressing m1 receptors: it enhances signalling by 77% at concentrations of 0.46 mmol litre^{-1}, had no significant effect at 0.70 mmol litre^{-1} and reduces signalling by 43% and 75% at desflurane concentrations of 0.92 mmol litre^{-1} and 1.66 mmol litre^{-1}, respectively. C: Desflurane has a biphasic effect on Mch-induced $I_{Cl(Ca)}$ m3 muscarinic signalling. it has no significant effect at concentrations of 0.46 mmol litre^{-1} but enhances signalling by 78% ($P=0.03$) at concentrations of 0.70 mmol litre^{-1}. No effect is seen at 0.92 mmol litre^{-1}, whereas signalling is inhibited at 1.66 mmol litre^{-1} ($P<0.001$). $^{**}P<0.01$, $^{***}P<0.001$ (ANOVA, *t* test).

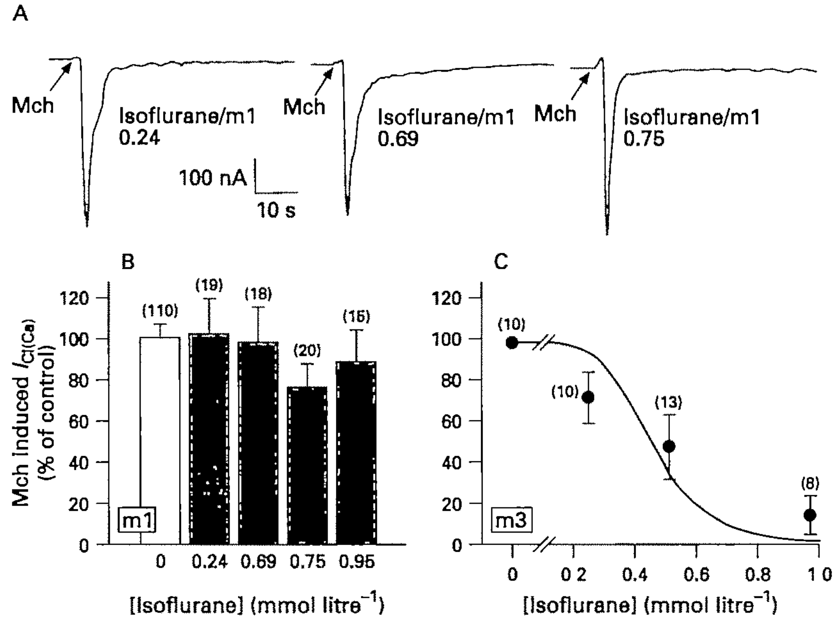

Figure 3 Influence of isoflurane on m1 and m3 muscarinic signalling. A. $I_{Cl(Ca)}$ induced by Mch 10^{-7} mol litre^{-1} in oocytes expressing m1 receptors at various isoflurane concentrations: isoflurane 0.24 mmol litre^{-1}(1.5 μC), 0.69 mmol litre^{-1} (1.7 μC) and 0.75 mmol litre^{-1} (1.4 μC). B: Isoflurane had no effect on Mch-induced $I_{Cl(Ca)}$ signalling in oocytes expressing m1 receptors (average control response 1.6 μC; number of oocytes tested in parentheses). C: Concentration–inhibition relationship of isoflurane on m3 muscarinic signalling. Fitting values are given in table 1

the m1 receptor appeared to display higher sensitivity to the inhibitory effects of halothane and sevoflurane.

ANGIOTENSIN II AND MUSCARINIC RECEPTORS SHARED THE SAME INTRACELLULAR SIGNALLING PATHWAY

As we wished to study the effects of the anaesthetics on angiotensin signalling to localize their site of action, it was necessary to demonstrate that angiotensin and muscarinic receptors signal through the same pathway. We have shown previously that AT_{1A} receptors expressed in *Xenopus* oocytes signal through the IP_3 pathway, as signalling can be blocked specifically by intracellular microinjection of the IP_3 receptor antagonist heparin.[29] To confirm the experiments reported previously, and to determine if muscarinic signalling uses the same pathway, we evaluated the effect on signalling of microinjection of

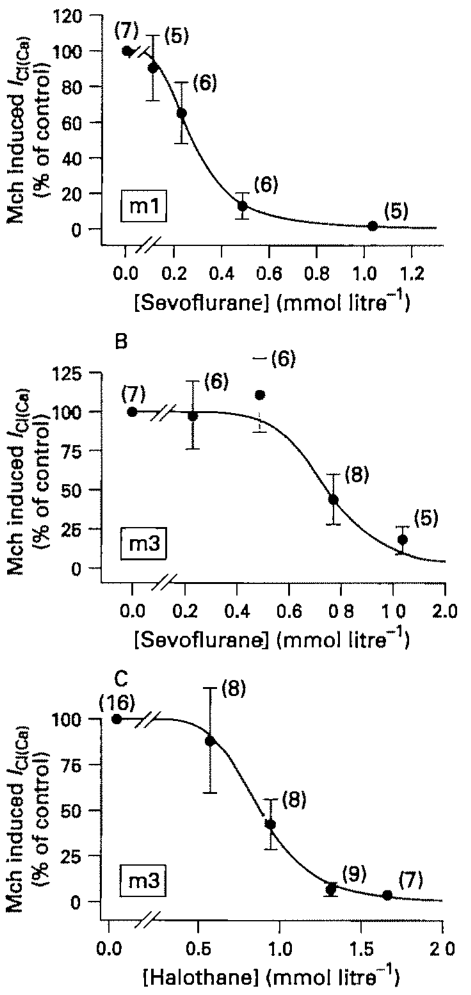

Figure 4 Influence of sevoflurane and halothane on m1 and m3 muscarinic signalling. Average control response 3.4 µC for m1 and 5.0 µC for m3 muscarinic receptors; number of oocytes tested in parentheses. A: Concentration–inhibition relationship of sevoflurane on m1 muscarinic signalling. Calculated IC$_{50}$ is 0.32 µmol litre^{-1}, Hill coefficient is 3.5. B: Concentration–inhibition relationship of sevoflurane on m3 muscarinic signalling. Calculated IC$_{50}$ is 0.75 µmol litre^{-1}, Hill coefficient is 6.8. C: Concentration–inhibition relationship of halothane on m3 muscarinic signalling. Fitting values are given in table 1.

heparin (2 ng nl^{-1}, 60 nl, 30 min before recording) into oocytes expressing m1 or AT$_{1A}$ receptors. m1 muscarinic signalling was inhibited to the same degree as angiotensin signalling (fig. 5A). Heparin microinjection into the oocyte inhibited responses to Mch by 93% compared with controls (fig. 5B). In contrast, microinjected water had no effect on either muscarinic or angiotensin signalling (data not shown). As the oocyte expresses only a single isoform of phospholipase C, coupling receptor activation to intracellular Ca^{2+} release,[21] our findings indicate that the muscarinic and AT$_{1A}$ signalling pathways are identical downstream of the G protein (compare fig. 1A).

SITE OF ACTION: VOLATILE ANAESTHETICS HAD NO EFFECT ON ANGIOTENSIN SIGNALLING

As muscarinic and angiotensin signalling use the same intracellular second messenger pathways, we investigated the effect of desflurane, isoflurane and sevoflurane on AT$_{1A}$ receptor function. In contrast with their variable effects on m1 and m3 signalling, the anaesthetics used had no effect on AT$_{1A}$ signalling, even at high concentrations (fig. 5C). Similar results were reported for halothane.[13] These results indicate that the actions of these anaesthetics on m1 and m3 signalling are not mediated by effects on the intracellular pathways, as these are shared by muscarinic and angiotensin receptors.

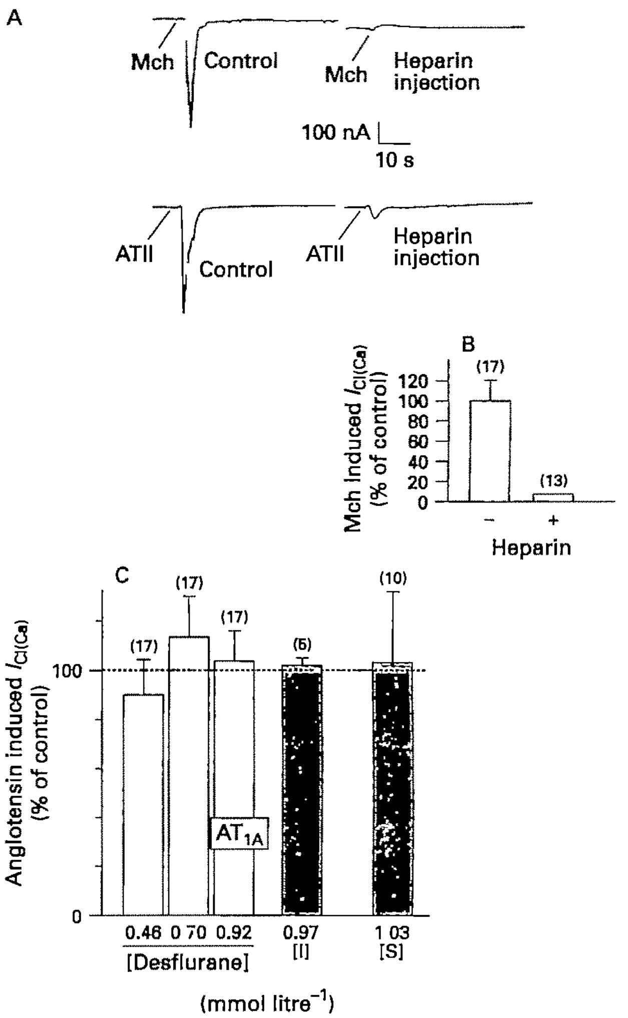

Figure 5 Heparin blocks muscarinic and angiotensin signalling. A: Top: Response of a control oocyte to Mch 10^{-7} mol litre^{-1} (1.4 µC), and lack of response after microinjection (30 min prior) of heparin 120 ng in a 60-nl volume. Bottom: Angiotensin II (ATII) signalling is similarly inhibited by prior microinjection of heparin. B: Mch-induced $I_{Cl(Ca)}$ is blocked by heparin microinjection 30 min prior to agonist application. + and – refer to oocytes injected and not injected with heparin, respectively (average control response 1.6 µC; number of oocytes tested in parentheses) (P<0.001 (t test). C: Desflurane, sevoflurane [S] and isoflurane [I], in common with halothane,[13] had no effect on angiotensin II signalling.

SITE OF ACTION: VOLATILE ANAESTHETICS HAD NO EFFECT ON IP$_3$-INDUCED CL$^-$ CURRENTS

To elucidate further the site of action of volatile anaesthetics on muscarinic signalling, we determined the effect of the anaesthetics on currents induced by microinjected IP$_3$ (50 nl of 2 mmol litre^{-1}, yielding approximately 100 µmol litre^{-1} intracellularly). IP$_3$-induced Cl$^-$ currents resembled the responses induced by receptor activation (fig. 6A). In contrast, microinjected water was ineffective (fig. 6B). Desflurane, even at high concentrations, had no effect on IP$_3$-induced currents, indicating that this

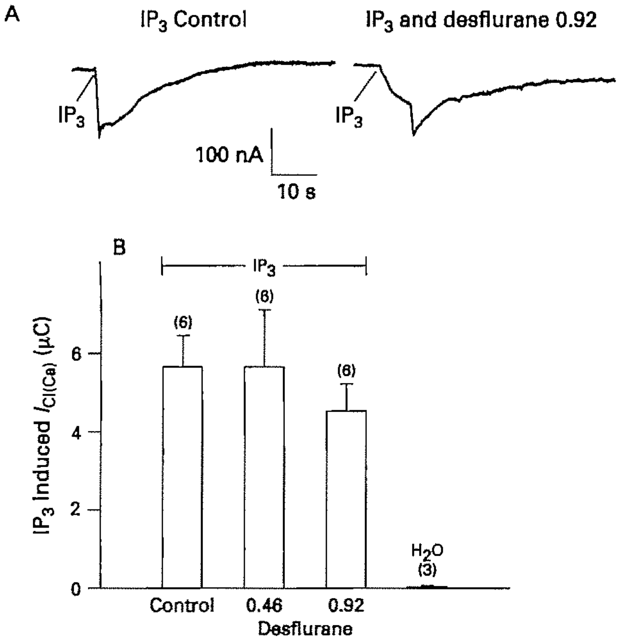

Figure 6 Inositoltrisphospate (IP$_3$) signalling is not inhibited by high concentrations of desflurane. A: Left: 50 nl of IP$_3$ injected (final intracellular concentration 100 µmol litre^{-1}) induced an $I_{Cl(Ca)}$ resembling responses generated by Mch or AT (compare fig. 1B, 1C). Right: Desflurane 0.92 mmol litre^{-1} had no effect on the oocyte response to IP$_3$. B: Desflurane 0.46 and 0.92 mmol litre^{-1} had no effect on $I_{Cl(Ca)}$ generated by intracellular IP$_3$ injection (average control response 1.3 µC; number of oocytes tested in parentheses). Injection of vehicle (H$_2$O) into the oocyte did not induce currents.

agent affects the signalling pathway before interaction between IP$_3$ and its receptor (fig. 6B). Similarly, we have shown that halothane, isoflurane and sevoflurane have no effect on intracellular IP$_3$ signalling or signalling induced by direct G-protein activation with GTPγS.[30]

REVERSIBILITY OF ANAESTHETIC ACTION

To complete this investigation, we determined the reversibility of anaesthetic inhibition of muscarinic signalling. Data are presented in figure 7. In all cases, anaesthetic inhibition was reversible on wash-out.

Discussion

Muscarinic signalling by m1 and m3 receptors was inhibited in a differential manner by the volatile anaesthetics studied. Halothane and sevoflurane, in clinically relevant concentrations, inhibited muscarinic signalling, with the m1 receptor displaying a higher sensitivity than the m3 receptor. Isoflurane had no effect on m1 muscarinic signalling, even at concentrations which would be anticipated to disrupt membrane structure,[28] but significantly inhibited m3 signalling. Desflurane showed a biphasic effect on both receptors.

Differences in effect between desflurane and isoflurane are remarkable, as the two compounds differ only in a single halogen atom: a chlorine atom in isoflurane is replaced by a fluorine atom in desflurane. Thus minor changes in chemical structure can induce significant pharmacological effects.

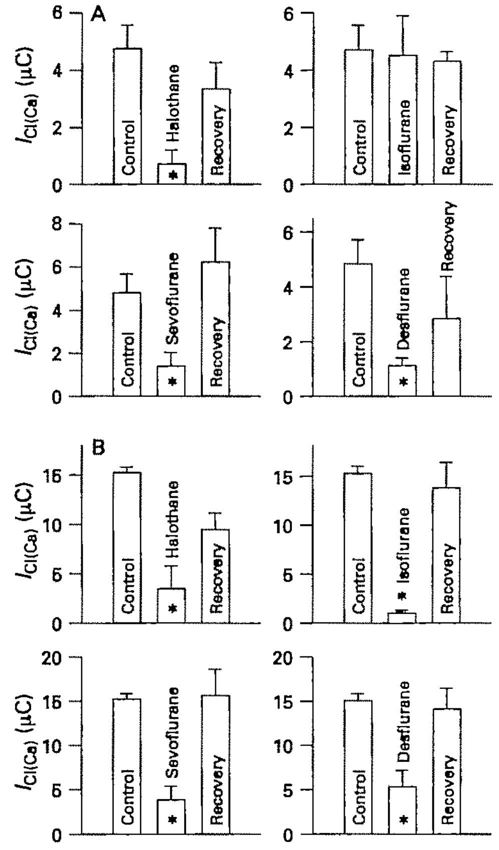

Figure 7 Reversibility of anaesthetic actions on muscarinic receptor signalling. A: $I_{Cl(Ca)}$ induced by Mch 10^{-4} mol litre^{-1} to determine reversibility of inhibition of volatile anaesthetics on m1 muscarinic acetylcholine receptor signalling. The first bar represents control measurements (4.83 (0.86) µC) and the second bar shows the inhibitory effect of the volatile anaesthetic tested (2.5% halothane, 3.3% isoflurane, 5% sevoflurane and 18% desflurane). $I_{Cl(Ca)}$ was reduced to 14% (0.7 (0.15) µC), 96.6% (4.64 (1.45) µC), 28.15% (1.36 (0.78) µC) and 24% (1.16 (0.27) µC) by halothane, isoflurane, sevoflurane and desflurane, respectively. The third bar shows recovery after 10 min of perfusion with Tyrode's solution without anaesthetic ($^*P<0.05$, *t* test). B: $I_{Cl(Ca)}$ induced by Mch 10^{-6} mol litre^{-1} to determine reversibility of inhibition of volatile anaesthetics on m3 muscarinic acetylcholine receptor signalling. Three consecutive measurements were made in different oocytes. The first bar represents control measurements (15 2 (0.67) µC) and the second bar shows the inhibitory effect of the volatile anaesthetic tested (2.5% halothane, 3.3% isoflurane, 5% sevoflurane, 18% desflurane). $I_{Cl(Ca)}$ was reduced to 22% (3.43 (2.25) µC), 6.5% (0.93 (0.33) µC), 25% (3.8 (1.55) µC) and 37% (5.58 (1.88) µC) by halothane, isoflurane, sevoflurane and desflurane, respectively. The third bar shows recovery after 10 min of perfusion with Tyrode's solution without anaesthetic ($^*P<0.05$, *t* test).

The biphasic action of desflurane on muscarinic signalling is unusual, although not unprecedented. Ryanodine[31] and adenosine[32] are known to act similarly in various models. Our study was not designed to determine the molecular mechanism of this biphasic action. However, we could rule out interactions with the intracellular signalling pathway, as none of the anaesthetics had effects on both AT and IP$_3$ signalling. Hence the site of action is most likely at the muscarinic receptor or (possibly) the associated G protein. Biphasic responses are explained most easily by the existence of two different binding sites at the receptor with different affinities and different agonistic–antagonistic effects when occupied. Mutagenesis studies may be able to delineate such various binding sites on the muscarinic receptor.

Our findings should be interpreted in view of the artificial environment in which the receptors were expressed. However, muscarinic and angiotensin receptors have been expressed frequently in the *Xenopus* oocyte model system, both by ourselves[13 14] and others,[33 34] and it is well established that they function similarly in oocytes as they do in native cells. Although the receptors are expressed at a lower temperature than they are normally exposed to, this has not been shown to result in significant changes in kinetics or function.

Any attempt to correlate our findings to observed clinical effects of anaesthetics is arduous, as conclusions drawn from several receptor subtypes cannot be transferred to a complex organism and its response to anaesthesia. Although most clinical and experimental data comparing isoflurane and desflurane show a congruence in their CNS[35 36] and circulatory effects,[37–39] some unexplained differences exist. Desflurane is known to exhibit less negative inotropic activity and to induce smaller decreases in arterial pressure.[39] When heart rate, mean arterial pressure and sympathetic nerve activity were compared after 10.9% desflurane anaesthesia 2 min after induction in humans, all variables were enhanced significantly compared with isoflurane[17]; after more prolonged anaesthesia there were no differences between the anaesthetics. This initial period of excitation, when anaesthetic concentrations are relatively low, could result potentially from interactions with muscarinic signalling pathways. It would be of great interest to study the interactions between desflurane and adrenergic receptor functioning, as excitatory effects of desflurane directly on the β-adrenergic receptor or on presynaptic ganglia might also explain its excitatory effects.

CNS muscarinic stimulation raises the level of consciousness and improves learning.[3] It is interesting to speculate if stimulation of m1 signalling (the most prominent cerebral muscarinic subtype) by low desflurane concentrations might contribute to the rapid mental recovery observed with the anaesthetic.[40] If so, this might be of particular importance in elderly patients with limited CNS muscarinic signalling reserve (e.g. patients with Alzheimer's disease). The prominence of the m3 subtype in bronchial smooth muscle[41] and glands[1] could explain in part the irritating effect of desflurane during induction and emergence from anaesthesia, when anaesthetic concentrations are relatively low.

In brief, we have demonstrated that desflurane had a concentration-dependent biphasic effect on m1 and m3 muscarinic receptor functioning, whereas isoflurane had no effect on m1 signalling but pronounced effects on m3 signalling. We have also shown that halothane and sevoflurane inhibited m1 and m3 signalling in a dose-dependent manner. This action is most likely localized at the receptor level, as the anaesthetics did not influence intracellular signalling pathways. In addition, the anaesthetics had no effect on angiotensin signalling. In combination with our findings that halothane inhibits m1 signalling in a concentration-dependent manner,[13] these results show that different volatile anaesthetics affect m1 and m3 muscarinic signalling in highly divergent ways, and that small changes in chemical structure of the volatile anaesthetic or the receptor can significantly affect anaesthetic–protein interactions.

Acknowledgements

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References

1. Lodge D, Anis NA, Burton NR. Effects of optical isomers of ketamine on excitation of cat and rat spinal neurones by amino acids and acetylcholine. *Neuroscience Letters* 1982; **29**: 281–286.
2. Zaagsma J, Roffel AF, Meurs H. Muscarinic control of airway function. *Life Sciences* 1997; **60**. 1061–1068.
3. Durieux ME. Muscarinic signalling in the central nervous system: Recent developments and anesthetic implications. *Anesthesiology* 1996; **84**: 173–189.
4. Lucidi-Phillipi CA, Gage FH. The neurotrophic hypothesis and the cholinergic basal forebrain projection. *Progress in Brain Research* 1993; **98**: 241–249.
5. Price DL, Koliatsos VE, Clatterbuck RC. Cholinergic systems: human diseases, animal models, and prospects for therapy. *Progress in Brain Research* 1993; **98**: 51–60.
6. Gillberg P-G, Aquilonius S-M. Cholinergic, opioid and glycine receptor binding sites localized in human spinal cord by *in vitro* autoradiography; changes in amyotrophic lateral sclerosis. *Acta Neurologica Scandinavica* 1985; **72**: 299–306.
7. Scatton B, Dubois A, Javoy-Agid F, Camus A. Autoradiographic localization of muscarinic cholinergic receptors at various segmental levels of the human spinal cord. *Neuroscience Letters* 1984; **49**: 239–245.
8. Yamamoto K, Morimoto N, Warner DO, Rehder K, Jones KA. Factors influencing the direct actions of volatile anesthetics on airway smooth muscle. *Anesthesiology* 1993; **78**: 1102–1111.
9. Anthony BL, Dennison RL, Aronstam RS. Influence of volatile anesthetics on muscarinic regulation of adenylate cyclase activity. *Biochemical Pharmacology* 1990; **40**: 376–379.
10. Anthony BL, Dennison RL, Narayanan TK, Aronstam RS. Diethyl ether effects on muscarinic acetylcholine receptor complexes in rat brainstem. *Biochemical Pharmacology* 1988; **37**: 4041–4046.
11. Dennison RL, Anthony BL, Narayanan TK, Aronstam RS. Effects of halothane on high affinity agonist binding and guanine nucleotide sensitivity of muscarinic acetylcholine receptors from brainstem of rat. *Neuropharmacology* 1987; **26**: 1201–1205.
12. Anthony BL, Dennison RL, Aronstam RS. Disruption of muscarinic receptor-G protein coupling is a general property of liquid volatile anesthetics. *Neuroscience Letters* 1989; **99**: 191–196.
13. Durieux ME. Halothane inhibits signalling through m1 muscarinic receptors expressed in *Xenopus* oocytes. *Anesthesiology* 1995; **82**: 174–182.
14. Durieux ME. Inhibition by ketamine of muscarinic acetylcholine receptor function. *Anesthesia and Analgesia* 1995; **81**: 57–62.
15. Levey AI. Immunological localization of m1-m5 muscarinic acetylcholine receptors in peripheral tissues and brain. *Life Sciences* 1993; **52**: 441–448.
16. Vilaro MT, Mengod G, Palacios JM. Advances and limitations of the molecular neuroanatomy of cholinergic receptors: the example of multiple muscarinic receptors. *Progress in Brain Research* 1993; **98**: 95–101.
17. Ebert TJ, Muzi M. Sympathetic activation with desflurane in humans. *Advances in Pharmacology* 1994, **31**: 369–378.
18. Muzi M, Lopatka CW, Ebert TJ. Desflurane-mediated neurocirculatory activation in humans. Effects of concentration and rate of change on responses. *Anesthesiology* 1996; **84**: 1035–1042.
19. Weiskopf RB, Eger EI, Daniel M, Noorani M. Cardiovascular stimulation induced by rapid increases in desflurane concentration in humans results from activation of tracheopulmonary and systemic receptors. *Anesthesiology* 1995; **83**· 1173–1178.
20. Tigyi G, Dyer DL, Matute C, Miledi R. A serum factor that

activates the phosphotidylinositol phosphate signalling system in *Xenopus* oocytes. *Proceedings of the National Academy of Sciences USA* 1990; 87: 1521–1525.

21. Ma H-W, Blitzer RD, Healy EC, Premont RT, Landau EM, Iyengar R. Receptor-evoked Cl^- current in Xenopus oocytes is mediated through a ß-type phospholipase C; cloning a new form of the enzyme. *Journal of Biological Chemistry* 1993; **268**: 19915–19918.
22. Ferguson JE, Hanley MR. Phosphatidic acid and lysophosphatidic acid stimulate receptor-regulated membrane currents in the *Xenopus laevis* oocyte. *Archives of Biochemistry and Biophysics* 1992; 297: 388–392.
23. Durieux ME, Lynch KR. Signalling properties of lysophosphatidic acid. *Trends in Pharmacological Sciences* 1993; 14: 249–254.
24. Durieux ME. OoClamp: An IBM-compatible software system for the study of receptors expressed in *Xenopus* oocytes. *Computer Methods and Programs in Biomedicine* 1993; 41: 101–105.
25. Durieux ME, Salafranca MN, Lynch KR, Moorman JR. Lysophosphatidic acid induces a pertussis toxin-sensitive Ca^{2+}-activated Cl^- current in *Xenopus laevis* oocytes. *American Journal of Physiology* 1992; 263: C896–900.
26. Renzi F, Waud BE. Partition coefficients of volatile anesthetics in Kreb's solution. *Anesthesiology* 1977; 47: 62–63.
27. Miao N, Lynch C. Effect of temperature on volatile anesthetic depression of myocardial contractions. *Anesthesia and Analgesia* 1993; 76: 366–371.
28. Smith RA, Porter EG, Miller KW. The solubility of anesthetic gases in lipid bilayers. *Biochimica et Biophysica Acta* 1981; 645: 327–338.
29. Chan CK, Durieux ME. Effects of halothane and isoflurane on lysophosphatidate signalling. *Anesthesiology* 1997; 86: 660–669.
30. Hoenemann CW, Nietgen GW, Podranski TA, Chan CK, Durieux ME. Influence of volatile anesthetics on thromboxane A_2 signalling. *Anesthesiology* 1998; 88: 440–451.
31. Ayabe T, Kopf GS, Schultz RM. Regulation of mouse egg activation: presence of ryanodine receptors and effects of microinjected ryanodine and cyclic ADP ribose on uninseminated and inseminated eggs. *Development* 1995; 121: 2233–2244.
32. Knecht M, Darbon JM, Ranta T, Baukal A, Catt KJ. Inhibitory actions of adenosine on follicle-stimulating hormone- induced differentiation of cultured rat granulosa cells. *Biological Reproduction* 1984; 30: 1082–1090.
33. Kubo T, Fukuda K, Mikami A, Maeda A, Takahashi H, Mishina M, Haga T, Haga K, Ichiyama A, Kangawa K, Kojima M, Matsuo H, Hirose T, Numa S. Cloning, sequencing and expression of complementary DNA encoding the muscarinic acetylcholine receptor. *Nature (London)* 1986; 323: 411–416.
34. Lin LH, Leonard S, Harris A. Enflurane inhibits the function of mouse and human brain phosphatidylinositol-linked acetylcholine and serotonin receptors expressed in *Xenopus* oocytes. *Molecular Pharmacology* 1993; 43: 941–948.
35. Young WL. Effects of desflurane on the central nervous system. *Anesthesia and Analgesia* 1992; 75. S32–37.
36. Jones RM, Cashman JN, Mant TG. Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers. *British Journal of Anaesthesia* 1990; 64: 11–15.
37. Warltier DC, Pagel PS. Cardiovascular and respiratory actions of desflurane: is desflurane different from isoflurane? *Anesthesia and Analgesia* 1992; 75 (Suppl): S17–29.
38. Weiskopf RB, Eger EI, Noorani M, Daniel M. Repetitive rapid increases in desflurane concentration blunt transient cardiovascular stimulation in humans. *Anesthesiology* 1994; 81: 843–849.
39. Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Comparison of the systemic and coronary hemodynamic actions of desflurane, isoflurane, halothane, and enflurane in the chronically instrumented dog. *Anesthesiology* 1991; 74: 539–551.
40. Patel SS, Goa KL. Desflurane. A review of its pharmacodynamic and pharmacokinetic properties and its efficacy in general anaesthesia. *Drugs* 1995; 50: 742–767.
41. Simon RP, Griffiths T, Evans MC, Swan JH, Meldrum BS. Calcium overload in selectively vulnerable neurons of the hippocampus during and after ischemia; an electron microscopy study in the rat. *Journal of Cerebral Blood Flow and Metabolism* 1984; 4: 350–361.

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Effects of isoflurane on receptor-operated Ca^{2+} channels in rat aortic smooth muscle

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Summary

We have investigated the effects of isoflurane on receptor-operated Ca^{2+} channels (ROC) in vascular smooth muscle. In isolated rat thoracic aortic rings denuded of endothelium, the effects of isoflurane on phenylephrine-induced contraction and Ca^{2+} influx were evaluated in the presence of supramaximal doses of nifedipine or verapamil. Under isometric tension recording, the aortic rings were precontracted by phenylephrine 300 nmol litre^{-1} and exposed to 1.2%, 2.3% or 3.5% isoflurane. Phenylephrine-induced precontraction was enhanced with 2.3% isoflurane by mean 8.1 (SD 9.3) % ($P<0.05$ *vs* 0% isoflurane). The constrictor effect of 2.3% isoflurane was not inhibited by depletion of intracellular Ca^{2+} stores with ryanodine 20 μmol litre^{-1}, but was abolished in a Ca^{2+}-free solution or by SK&F 96365 30 μmol litre^{-1}, an ROC blocker. Isoflurane-induced contraction was accompanied by increased intracellular free Ca^{2+} concentration, monitored using fura PE3. Unidirectional $^{45}Ca^{2+}$ influx measurement in phenylephrine-stimulated aortic strips revealed that the mean amount of Ca^{2+} influx was significantly ($P<0.05$) enhanced by 1.2% and 2.3% isoflurane, which were 117.1% and 119.7% of control values, respectively. Our results strongly suggest that isoflurane enhanced Ca^{2+} influx through ROC that had been submaximally activated by phenylephrine. (*Br. J. Anaesth.* 1998; **81**: 578–583).

Keywords: anaesthetics volatile, isoflurane, sympathetic nervous system, phenylephrine; ions, calcium; ions, ion channels; muscle vascular pharmacology; rat

Halogenated volatile anaesthetics, including halothane, enflurane and isoflurane, modulate vascular contractility via a variety of mechanisms. These anaesthetics have been suggested to reduce Ca^{2+} influx into vascular smooth muscle cells because electrophysiological studies have shown that they suppress the activity of voltage-operated Ca^{2+} channels.[1–3] However, little information is available on the effect of anaesthetics on receptor-operated Ca^{2+} channels (ROC), the other pathways of Ca^{2+} influx.

The presence of ROC was first postulated in a review by Bolton,[4] who described them as voltage-insensitive Ca^{2+}-conducting channels in smooth muscle cells activated by receptor agonists such as norepinephrine (noradrenaline), acetylcholine or prostaglandins. It has also been shown that ROC are resistant to blockers of voltage-operated Ca^{2+} channels (VOC) such as nifedipine, verapamil or D600.[5–9] Although their electrophysiological properties and molecular structures are not yet established, it is clear that they are important pathways of Ca^{2+} influx in addition to VOC[10 11] and hence may play a key role in physiological vascular contraction.

Therefore, we attempted to elucidate the effect of isoflurane on ROC in vascular smooth muscle. Rat thoracic aorta was denuded of endothelium to eliminate its effect on smooth muscle contractility and pretreated with supramaximal doses of VOC blockers to exclude the effect of VOC which are sensitive to anaesthetics. Rings were stimulated with a submaximal dose of phenylephrine, an adrenergic α_1 receptor agonist to activate smooth muscle cell ROC. In this preparation, we estimated the effects of isoflurane by recording tension and intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) and by measuring unidirectional Ca^{2+} influx using $^{45}Ca^{2+}$. We suggest that isoflurane enhances Ca^{2+} influx through ROC.

Materials and methods

TISSUE PREPARATION

The study was approved by the Kyoto University Animal Use Committee. Male Wistar rats (250–350 g) were anaesthetized with pentobarbital (pentobarbitone) 50 mg kg^{-1} i.p. and killed by exsanguination. The descending part of the thoracic aorta was isolated and cut into rings, 5–6 mm for tension recording, 2 mm for $[Ca^{2+}]_i$ monitoring and 7–9 mm for $^{45}Ca^{2+}$ influx measurement. The endothelium was removed by rotating the rings around a rough surfaced needle. In tension experiments, endothelial denudation was confirmed by the inability of acetylcholine 10 μmol litre^{-1} to cause relaxation in rings precontracted by KCl 30 mmol litre^{-1}.

ISOMETRIC TENSION RECORDING

The aortic rings were mounted vertically in organ baths (37°C) containing 10 ml of Krebs–Ringer solution (KRS) aerated with a 95% oxygen–5% carbon

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dioxide gas mixture. Isometric tension was recorded with a force displacement transducer (San-ei, Tokyo, Japan). The rings were allowed to equilibrate for 60 min under a resting tension of 3 g, followed by contraction induced by adding KCl 30 mmol litre^{-1} and an acetylcholine test (10 μmol litre^{-1}). Thereafter, the rings were incubated for 10 min in KRS containing nifedipine 10 μmol litre^{-1}, which is supramaximal for blocking VOC in rat aortic smooth muscle cells.[7] In our preliminary study, this dose was sufficient to abolish completely KCl (30 mmol litre^{-1})-induced contraction. Submaximal contraction was then induced by adding phenylephrine 300 nmol litre^{-1} into the bath. When precontraction by phenylephrine was stabilized (15–20 min after addition), isoflurane vaporized with an Isotec3 (Ohmeda, England) was introduced to the 95% oxygen–5% carbon dioxide gas mixture supplied to the bath and maintained for 15 min. The concentration of isoflurane in the gas was monitored with an Atom 303 anaesthetic agent monitor (Atom, Tokyo, Japan) and adjusted to either 0% (control), 1.2%, 2.3% or 3.5%, which are the 0, 1, 2 and 3 minimum alveolar concentrations (MAC) in humans,[12] respectively. We used MAC for humans as an arbitrary unit of concentration of isoflurane. MAC for isoflurane in rats determined in a previous study was 1.27.[13] In our previous study,[14] a concentration of 2.3% isoflurane in the bath solution was assayed by gas chromatography and reached a stable level at mean 0.56 (SEM 0.00) mmol litre^{-1} (n=3) within 3–5 min after introduction to the gas line. The increase in tension induced by phenylephrine just before introduction of isoflurane was taken as 100%, and the effect of isoflurane was expressed as change in tension 10 min after introduction of isoflurane in each ring.

In some rings, experimental conditions were modified to control Ca^{2+} movements in smooth muscle. To deplete intracellular Ca^{2+} stores, we used ryanodine, a plant alkaloid that locks the Ca^{2+}-induced Ca^{2+}-release channel of sarcoplasmic reticulum in an open state, causing depletion of caffeine-sensitive Ca^{2+} stores.[15] While norepinephrine-sensitive Ca^{2+} stores may contain ryanodine-insensitive portions in other cell types,[15] in the rat aorta it has been shown to be depleted also by ryanodine.[5,16] Thus this treatment should lead to complete or near complete depletion of intracellular Ca^{2+} stores. Nifedipine-treated rings were exposed to ryanodine 20 μmol litre^{-1} and then to caffeine 25 mmol litre^{-1}. After transient caffeine-induced contractions terminated, caffeine was removed by replacing the bath solution with KRS containing ryanodine 20 μmol litre^{-1} and nifedipine 10 μmol litre^{-1}. After 5–10 min, the rings were precontracted with phenylephrine 300 nmol litre^{-1} and exposed to 0% (control) or 2.3% isoflurane. In other experiments, Ca^{2+} influx was excluded either by removing extracellular Ca^{2+} or by using an ROC blocker. To remove extracellular Ca^{2+}, the rings were incubated for 10 min in Ca^{2+}-free KRS containing EGTA 1 mmol litre^{-1} and nifedipine 10 μmol litre^{-1}, precontracted with phenylephrine 300 nmol litre^{-1}, and 10 min later, exposed to 2.3% isoflurane. To block ROC, SK&F 96365 30 μmol litre^{-1}, an ROC blocker in vascular smooth muscles,[11,17] was included in the bath solution during the pretreatment period with nifedipine, followed by application of phenylephrine and isoflurane as above.

SIMULTANEOUS TENSION RECORDING AND [CA^{2+}]$_i$ MONITORING

To monitor [Ca^{2+}]$_i$, we used a Ca^{2+}-sensitive fluorescent dye, fura PE3, a derivative of fura 2 with a lower rate of leak from inside the cell.[18] The rings were bathed in KRS containing fura PE3-AM 1 μmol litre^{-1}, a cell-permeant acetoxymethyl ester of fura PE3, and 0.02% vol/vol Cremophor EL, a non-cytotoxic detergent, for 4–6 h at 25°C. After rinsing, the rings were mounted horizontally in an organ bath (37°C) containing KRS 7 ml aerated with a 95% oxygen–5% carbon dioxide gas mixture. Isometric tension was recorded with a force-displacement transducer (San-ei, Tokyo, Japan) and fluorescence intensity was monitored using a dual wavelength fluorometer (CAF-110, Japan Spectroscopic, Tokyo, Japan) as described previously.[14] The rings were illuminated alternately with excitation light at wavelengths of 340 nm and 380 nm. The fluorescence emitted was detected through a 500-nm bandpass filter. Fluorescence intensities at 340 nm (F$_{340}$) and 380 nm (F$_{380}$) excitation corresponded to the amount of Ca^{2+}-bound fura PE3 and Ca^{2+}-free fura PE3, respectively. Therefore, the F$_{340}$/F$_{380}$ ratio was used as an indicator of [Ca^{2+}]$_i$. The rings were allowed to equilibrate for 60 min under a resting tension of 1 g, followed by contraction induced by KCl 30 mmol litre^{-1} and an acetylcholine test (10 μmol litre^{-1}). The rings were then incubated for 10 min in KRS containing verapamil 10 μmol litre^{-1} which was a supramaximal dose for blocking VOC in rat aorta in a previous ^{45}Ca^{2+} influx study[19] in addition to our previous KCl-contraction study. Verapamil was used in this experiment because nifedipine interfered with the excitation light for fura PE3. The rings were then precontracted with phenylephrine 300 nmol litre^{-1}. After 10 min, 2.3% isoflurane was introduced and maintained for 15 min. Isoflurane was vaporized and delivered as described above. The increase in tension and F$_{340}$/F$_{380}$ ratio induced by phenylephrine just before introduction of isoflurane were taken as 100%, and the effects of isoflurane were expressed as percentage change in tension and F$_{340}$/F$_{380}$ value, 10 min after introduction of isoflurane.

^{45}CA^{2+} INFLUX MEASUREMENT

For measuring unidirectional Ca^{2+} influx, we performed experiments according to a method described previously.[20] The aortic rings were cut open into strips and bathed in HEPES-buffered saline solution (HBS) bubbled with air for 60 min at 37°C. The strips were then incubated for 30 min at 37°C in HBS containing nifedipine 10 μmol litre^{-1} and transferred into a vial filled with 4 ml of HBS containing ^{45}Ca^{2+} 1 μCi ml^{-1}, nifedipine 10 μmol litre^{-1} and phenylephrine 300 nmol litre^{-1}. Isoflurane, vaporized and adjusted to 0% (control), 1.2%, 2.3% or 3.5%, as described above, had been delivered to the air supplied to the vial for at least 15 min before the strips were transferred into the vial. The strips were exposed to ^{45}Ca^{2+}-labelled HBS for 5 min at 37°C during maintained delivery of isoflurane with air. The amount of ^{45}Ca^{2+} taken into the tissue during such a short period can be assumed to be a result of Ca^{2+} influx, and back flow of ^{45}Ca^{2+} out of the cell can be regarded as negligible.[20] At the end of exposure to $^{45}Ca^{2+}$, the strips were bathed for 50 min in ice-cold Ca^{2+}-free HBS containing EGTA 2 mmol litre^{-1} to remove extracellular $^{45}Ca^{2+}$. The strips were then blotted, weighed and incubated overnight in 1.5 ml of EDTA 5 mmol litre^{-1} at room temperature. Finally, a 3-ml scintillation cocktail (Scintisol EX-H, Dojindo, Kumamoto, Japan) was added and analysed for $^{45}Ca^{2+}$ using a liquid scintillation counter. Data were expressed as amount of Ca^{2+} influx (μmol) per kg aorta (wet weight). As a control experiment, the strips were exposed to $^{45}Ca^{2+}$-labelled HBS without phenylephrine for each concentration of isoflurane.

SOLUTIONS AND DRUGS

The Krebs–Ringer solution had the following composition (mmol litre^{-1}): NaCl 120, KCl 5.0, $CaCl_2$ 2.0, $MgCl_2$ 1.0, $NaHCO_3$ 25.0 and glucose 5.5; pH of the solution was 7.3 when the solution was aerated with a 95% oxygen–5% carbon dioxide gas mixture. The HBS solution had the following composition (mmol litre^{-1}): NaCl 140, KCl 5.0, $CaCl_2$ 2.0, $MgCl_2$ 1.0, glucose 5.5, HEPES 5.0; pH adjusted to 7.3 with NaOH. The solution was air-bubbled throughout the experiments. The drugs used were isoflurane (Dainabot, Tokyo, Japan), fura PE3-AM (Dojindo, Kumamoto, Japan), Cremophor EL, phenylephrine and nifedipine (Sigma), acetylcholine (Daiichi Pharmaceutical Co., Tokyo, Japan), pentobarbital, verapamil, EGTA (ethylene glycol bis-N,N,N',N'-tetraacetic acid), EDTA (ethylenediaminetetraacetic acid), caffeine (Nacalai Tesque, Kyoto, Japan), ryanodine (Wako Pure Chemical Industries, Osaka, Japan) and SK&F 96365 (BIOMOL, PA, USA).

STATISTICAL ANALYSIS

All data are presented as mean (SD); *n* represents the number of rings examined in each group. Rings from an animal were assigned to different groups, and therefore each group did not contain rings from the same animal. When single doses (2.3%) were tested, the effects of isoflurane were compared with control (0%) using Student's *t* test. When multiple doses of isoflurane were tested, data were analysed by one-way factorial ANOVA. If the *F* test indicated significance ($P<0.05$), the effect of each dose of isoflurane was compared with control using Fisher's PLSD test for *post hoc* comparison. Differences at $P<0.05$ were considered significant.

Results

EFFECT OF ISOFLURANE ON PHENYLEPHRINE-INDUCED CONTRACTION

Phenylephrine induced sustained contraction (0.93 (0.44) g, $n=48$) which was not different between groups for each concentration of isoflurane. After administration of 1.2% or 2.3% isoflurane, an additional contraction developed slowly, which was sustained during isoflurane delivery and disappeared after its termination (fig. 1A, B). However, contraction induced by 3.5% isoflurane was transient and was followed by relaxation to a varying extent (fig. 1C). At 10 min after administration of 2.3% isoflurane, a maximal contraction was elicited (8.1 (9.3) %, $n=12$), which was significantly larger ($P<0.05$) than that in controls (–2.4 (6.8) %, $n=12$). Contraction by isoflurane was not linearly dose-related because contraction with 3.5% isoflurane was smaller than that with 2.3% (fig. 1D). In the following experiments, the effects of isoflurane were examined at 2.3% which elicited the maximal response.

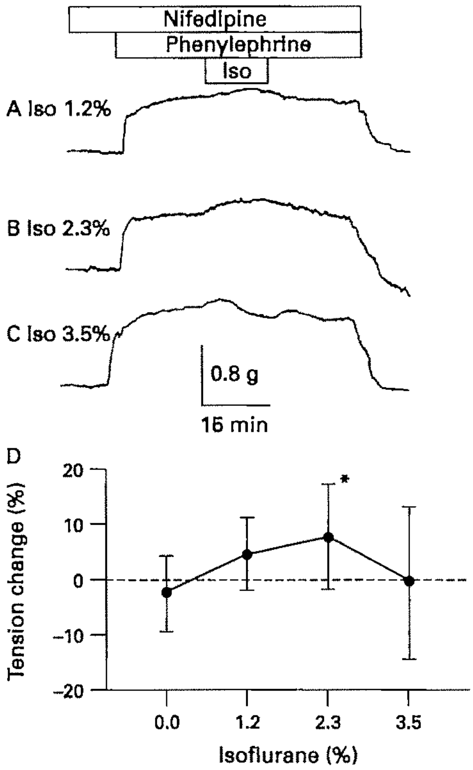

Figure 1 Tension changes in rat aortic rings during exposure to isoflurane after treatment with nifedipine 10 μmol litre^{-1} and phenylephrine 300 nmol litre^{-1}. Typical recordings with 1.2% (A), 2.3% (B) and 3.5% (C) isoflurane (Iso) are shown. Isoflurane (1.2% and 2.3%) increased contraction during delivery of isoflurane and contraction disappeared after its termination (A, B). Contraction induced by 3.5% isoflurane was transient and followed by relaxation (C). The effects of 10 min exposure to isoflurane on tension (D), with the increase in tension induced by phenylephrine taken as 100% is also shown. Isoflurane 2.3% elicited a significantly larger contraction (*$P<0.05$) than control.

When rings were treated with ryanodine combined with caffeine, a slow increase in tension was observed (fig. 2), which may have been caused by liberation of Ca^{2+} from sarcoplasmic reticulum[5 16] or enhanced Ca^{2+} influx.[16] Phenylephrine induced further contraction of the ring (0.18 (0.06) g, $n=14$), which was not different between control rings and rings treated with 2.3% isoflurane (fig. 2). Contraction produced by phenylephrine in such circumstances should be mediated by influx of Ca^{2+}, not by Ca^{2+} release.[16] The change in tension induced by 2.3% isoflurane was 13.8 (23.9) % ($n=7$), which was significantly larger ($P<0.01$) than that in controls (–24.0 (21.6) %, $n=7$).

In Ca^{2+}-free KRS containing EGTA 1 mmol litre^{-1}, phenylephrine-induced contraction was small and only transient, returning to resting tension within 5–7 min (fig. 3A). Subsequent exposure to 2.3% isoflurane for 10 min did not change the tension in any ring examined ($n=8$) (fig. 3A). In the presence of the ROC blocker SK&F 96365, phenylephrine-

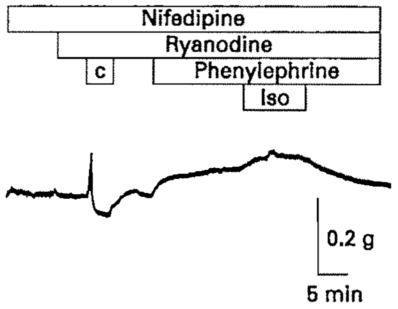

Figure 2 A typical recording of tension changes in rat aortic rings during exposure to 2.3% isoflurane (Iso) after treatment with ryanodine 20 µmol litre^{-1} and caffeine (c) 25 mmol litre^{-1} in the presence of nifedipine 10 µmol litre^{-1} and phenylephrine 300 nmol litre^{-1}. Isoflurane 2.3% enhanced phenylephrine-induced contraction.

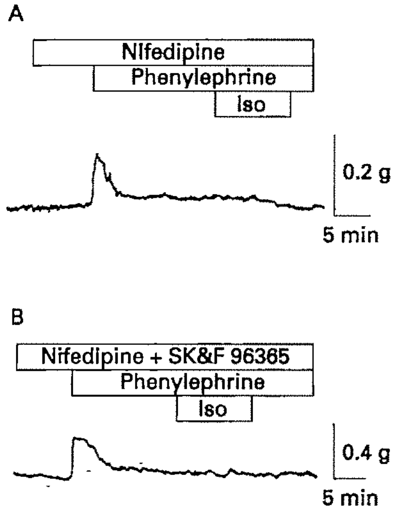

Figure 3 Typical recordings of tension changes in rat aortic rings during exposure to 2.3% isoflurane (Iso) in Ca^{2+}-free KRS containing EGTA 1 mmol litre^{-1} (A) and an SK&F 96365-containing solution (B). In both solutions, phenylephrine-induced contraction was only transient and the constrictor effect of 2.3% isoflurane was abolished.

induced contraction was similar to that in Ca^{2+}-free solution, that is reduced in size and transient (fig. 3B). Again, 2.3% isoflurane did not elicit contraction in any ring examined ($n=5$) (fig. 3B).

EFFECT OF ISOFLURANE ON $[CA^{2+}]_i$

Phenylephrine elicited a sustained contraction together with an increase in $[Ca^{2+}]_i$, as evaluated by the F_{340}/F_{380} value for fura PE3. Isoflurane 2.3% enhanced both tension and $[Ca^{2+}]_i$ responses to phenylephrine (fig. 4). The time courses of $[Ca^{2+}]_i$ during exposure to isoflurane were similar to those of contraction; sustained and reversible. Ten minutes after introduction, 2.3% isoflurane increased tension by 25.3 (13.2) % ($n=6$), which was significantly larger ($P<0.05$) than the increase in the control group (7.11 (8.0) %, $n=9$). In addition, the F_{340}/F_{380} ratio was increased with isoflurane by 34.9 (32.7) % ($n=6$), which was significantly larger ($P<0.05$) than that in the control (−6.1 (11.2) %, $n=9$).

EFFECT OF ISOFLURANE ON UNIDIRECTIONAL CA^{2+} INFLUX

In the control group (0% isoflurane), phenylephrine-stimulated strips showed significantly larger Ca^{2+} influx than strips not stimulated with phenylephrine ($P<0.01$) (fig. 5). In phenylephrine-stimulated groups, Ca^{2+} influx in groups exposed to 1.2% and 2.3% isoflurane were larger than in controls ($P<0.05$) (fig. 5). Increasing the concentration of isoflurane to 3.5% did not enhance Ca^{2+} influx further. In strips not stimulated with phenylephrine, isoflurane had no significant effect on Ca^{2+} influx at any concentration.

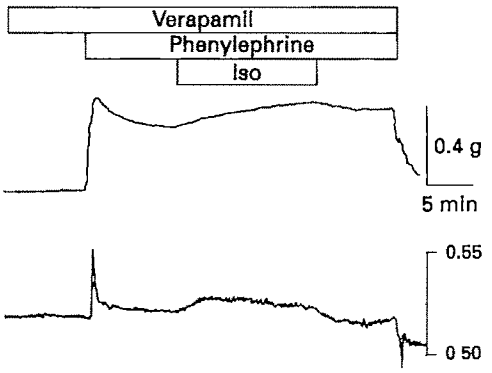

Figure 4 A typical recording of tension changes (top) and F_{340}/F_{380} ratio (bottom) in rat aortic rings during exposure to 2.3% isoflurane (Iso) after treatment with verapamil 10 µmol litre^{-1} and phenylephrine 300 nmol litre^{-1}. Isoflurane 2.3% enhanced both tension and F_{340}/F_{380} ratio.

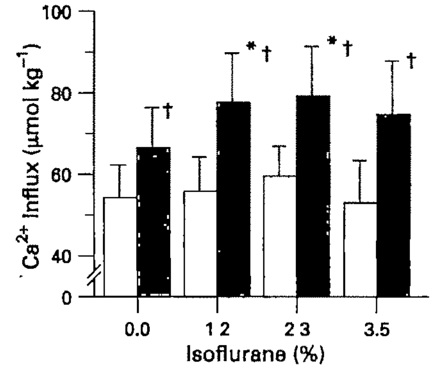

Figure 5 Modulation of Ca^{2+} influx by isoflurane in the presence of nifedipine 10 µmol litre^{-1} ($n=15$ each) after treatment with (solid bars) and without (control) (open bars) phenylephrine 300 nmol litre^{-1}. Isoflurane 1.2% and 2.3% significantly enhanced Ca^{2+} influx compared with control in phenylephrine-stimulated strips. Isoflurane 3.5% did not further enhance Ca^{2+} influx compared with 0% isoflurane. *$P<0.05$ compared with values without isoflurane; †$P<0.01$ compared with each value without phenylephrine.

Discussion

In this study, rat aortic rings were denuded of endothelium and exposed to supramaximal doses of VOC blockers, nifedipine or verapamil, throughout the experiments. In these rings, submaximal stimulation of the α_1 receptor by phenylephrine caused sustained contraction and an increase in $[Ca^{2+}]_i$. Isoflurane 2.3% enhanced these phenylephrine-induced responses. The constrictor effects of isoflurane were not abolished by Ca^{2+} store depletion caused by ryanodine and caffeine, but were abolished by removal of extracellular Ca^{2+} and by SK&F 96365. These results suggest that the constrictor effects were not a result of Ca^{2+} release from intracellular stores, but influx of extracellular Ca^{2+} through channels which are resistant to nifedipine and verapamil and sensitive to SK&F 96365. However, uncertainty remained in these experiments. Immersion of rings in Ca^{2+}-free solution may reduce intracellular Ca^{2+} stores[21] and may disturb the possible action of isoflurane in releasing intracellularly stored Ca^{2+}. Moreover, in both Ca^{2+}-removal and SK&F 96365 experiments, tension after transient precontraction by phenylephrine was near the resting level and the effects of subsequent administration of isoflurane may not have been evaluated correctly. Therefore, we performed $^{45}Ca^{2+}$ influx measurements to evaluate net Ca^{2+} movement through the cell membrane. The results revealed that 1.2% and 2.3% isoflurane significantly enhanced Ca^{2+} influx in phenylephrine-stimulated strips. The amount of Ca^{2+} influx was enhanced by 19.7% at 2.3% isoflurane, which may be enough to account for isoflurane-induced contraction. These results indicate that isoflurane enhanced Ca^{2+} influx through ROC which were activated by phenylephrine.

In the literature, release of stored Ca^{2+} has been the most commonly suggested mechanism for volatile anaesthetic-induced, endothelium-independent vasoconstriction.[14 22–24] Indeed, in verapamil-exposed rat[25] and rabbit[22] aortae, enhancement of norepinephrine-induced contraction by isoflurane has been demonstrated and ascribed to isoflurane-induced Ca^{2+} release. However, Ca^{2+} release induced by isoflurane has been shown to be much smaller than that induced by halothane or enflurane[26 27] or even undetectable.[14 23] Ryanodine, which effectively blocked anaesthetic-induced Ca^{2+} release in previous studies,[14 22–24] failed to inhibit isoflurane-induced contraction in our study, suggesting that contraction was not dependent on intracellular Ca^{2+} stores. It does not necessarily exclude the possibility of a minor contribution of Ca^{2+} release evoked by isoflurane. However, as contraction was undetectable in Ca^{2+}-free and SK&F 96365-containing solutions, it can be suggested that Ca^{2+} release by isoflurane is small, if present. In addition, it is unlikely that Ca^{2+} release by isoflurane itself stimulated Ca^{2+} influx to replete stores, which has been suggested in airway smooth muscle for halothane.[28] If this mechanism were prominent, isoflurane should have significantly increased Ca^{2+} influx even without phenylephrine in $^{45}Ca^{2+}$ experiments and the presence of phenylephrine would not have enhanced this process.

Previous studies using an established cell line of rat aortic smooth muscle cells (A7r5) failed to show activation of receptor-mediated Ca^{2+} influx by volatile anaesthetics.[29–31] In these studies, VOC blockers were not used, assuming that VOC did not contribute to receptor-mediated Ca^{2+} influx in the A7r5 cell. However, because the A7r5 cell has a dihydropyridine-sensitive VOC,[32] it is possible that the activity of VOC may have modulated Ca^{2+} influx in these studies. In contrast, Iaizzo[33] and Akata and Boyle[27] have suggested that isoflurane or halothane induce Ca^{2+} influx in A10 smooth muscle cell and rat mesenteric artery, respectively. However, as these studies were not designed to study Ca^{2+} influx, direct evidence of increased Ca^{2+} influx and characterization of the influx pathway are lacking. Thus our study is the first to provide direct evidence for stimulation of Ca^{2+} influx by volatile anaesthetics in vascular smooth muscle.

Several Ca^{2+} influx pathways consistent with the definition of ROC by Bolton[4] have been demonstrated in vascular smooth muscle; receptor-operated Ca^{2+} channel linked directly to ATP receptors in rabbit ear artery,[34] Ca^{2+}-permeable non-selective cation channels activated by norepinephrine[35] or endothelin-1[36] and Ca^{2+} influx activated by depletion of intracellular Ca^{2+} stores[37 38] which is often called "capacitative Ca^{2+} entry". Recently, at least two different Ca^{2+} influx pathways were demonstrated in A7r5 cells, one of which may depend on the capacitative mechanism.[38] In this study, we could not define the pathway activated by isoflurane as selective blockers to differentiate these pathways are not yet available. Electrophysiological studies using a patch-clamp technique are necessary for further analysis of the isoflurane-activated channel.

In both tension recording and $^{45}Ca^{2+}$ influx experiments, the effects of isoflurane were not linearly concentration-dependent, showing maximal effects at a concentration of 2.3%. Without phenylephrine, isoflurane itself could not induce significant Ca^{2+} influx in the $^{45}Ca^{2+}$ influx experiments. In addition, in our preliminary tension recording experiment, isoflurane did not induce contraction if the rings were not precontracted with phenylephrine (data not shown). These results suggest that isoflurane alone cannot activate Ca^{2+} influx sufficiently to induce contraction but can enhance Ca^{2+} influx that has been activated by phenylephrine. Further characterization of the isoflurane-activated channel would help to explain these properties of isoflurane.

In summary, this study strongly suggests that isoflurane enhanced stimulation of ROC by phenylephrine in rat aorta. This is a novel finding that could contribute to the understanding of regulation of vascular contractility caused by volatile anaesthetic. It is possible that this effect counteracts other vasodilating mechanisms of isoflurane, contributing to maintenance of vascular tone during anaesthesia.

References

1. Buljubasic N, Rusch NJ, Marijic J, Kampine JP, Bosnjak ZJ. Effects of halothane and isoflurane on calcium and potassium channel currents in canine coronary arterial cells. *Anesthesiology* 1992; 76: 990–998.
2. Buljubasic N, Flynn NM, Marijic J, Rusch NJ, Kampine JP, Bosnjak ZJ. Effects of isoflurane on K^+ and Ca^{2+} conductance in isolated smooth muscle cells of canine cerebral arteries. *Anesthesia and Analgesia* 1992; 75: 590–596.
3. Wilde DW. Isoflurane reduces Ca^{++} channel current and accelerates current decay in guinea pig portal vein smooth muscle cells. *Journal of Pharmacology and Experimental Therapeutics* 1994; 271: 1159–1166.
4. Bolton TB. Mechanisms of action of transmitters and other substances on smooth muscle. *Physiological Reviews* 1979; 59: 606–718.

5 Koch P, Wilffert B, Wilhelm D, Peters T. An approach to differentiate between noradrenaline-elicited contractile processes in the rat isolated aorta. *Naunyn-Schmiedeberg's Archives of Pharmacology* 1990; 342: 454–461.

6. Hester RK. Functional importance of alpha adrenoceptor-mediated, D600-insensitive Ca^{++} entry in rabbit aorta. *Journal of Pharmacology and Experimental Therapeutics* 1988; 247: 223–247.
7. Godfraind T. Actions of nifedipine on calcium fluxes and contraction in isolated rat arteries. *Journal of Pharmacology and Experimental Therapeutics* 1983; 224: 443–450.
8. Godfraind T, Miller RC. Specificity of action of Ca^{++} entry blockers. A comparison of their actions in rat arteries and in

human coronary arteries. *Circulation Research* 1983; **52** (Suppl. I): 81–91.

9. Simpson AWM, Stampfl A, Ashley CC. Evidence for receptor-mediated bivalent-cation entry in A10 vascular smooth-muscle cells. *Biochemical Journal* 1990; **267**: 277–280.
10. van Breemen C, Saida K. Cellular mechanisms regulating $[Ca^{2+}]_i$ smooth muscle. *Annual Review of Physiology* 1989; **51**: 315–329.
11. Komuro T, Miwa S, Zhang X, Minowa T, Enoki T, Kobayashi S, Okamoto Y, Ninomiya H, Sawamura T, Kikuta K, Iwamuro Y, Furutani H, Hasegawa H, Uemura Y, Kikuchi H, Masaki T. Physiological role of Ca^{2+}-permeable nonselective cation channel in endothelin-1-induced contraction of rabbit aorta. *Journal of Cardiovascular Pharmacology* 1997; **30**: 504–509.
12. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, de Jong RH, Elashoff RM. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
13. Rampil IJ, Mason P, Singh H. Anesthetic potency (MAC) is independent of forebrain structures in the rat. *Anesthesiology* 1993; **78**: 707–712.
14. Kakuyama M, Hatano Y, Nakamura K, Toda H, Terasako K, Nishiwada M, Mori K. Halothane and enflurane constrict canine mesenteric arteries by releasing Ca^{2+} from intracellular Ca^{2+} stores. *Anesthesiology* 1994; **80**: 1120–1127.
15. Iino M, Kobayashi T, Endo M. Use of ryanodine for functional removal of the calcium store in smooth muscle cells of the guinea-pig. *Biochemical and Biophysical Research Communications* 1988; **152**: 417–422.
16. Julou-Schaeffer G, Freslon JL. Effects of ryanodine on tension development in rat aorta and mesenteric resistance vessels. *British Journal of Pharmacology* 1988; **95**: 605–613.
17. Minowa T, Miwa S, Kobayashi S, Enoki T, Zhang XF, Komuro T, Iwamuro Y, Masaki T. Inhibitory effect of nitrovasodilators and cyclic GMP on ET-1-activated Ca^{2+}-permeable nonselective cation channel in rat aortic smooth muscle cells. *British Journal of Pharmacology* 1997; **120**: 1536–1544.
18. Vorndran C, Minta A, Poenie M. New fluorescent calcium indicators designed for cytosolic retention or measuring calcium near membranes. *Biophysical Journal* 1995; **69**: 2112–2124.
19. Karaki H, Nakagawa H, Urakawa N. Comparative effects of verapamil and sodium nitroprusside on contraction and ^{45}Ca uptake in the smooth muscle of rabbit aorta, rat aorta and guinea-pig taenia coli. *British Journal of Pharmacology* 1984; **81**: 393–400.
20. Meisheri KD, Hwang O, van Breemen C. Evidence for two separate Ca^{2+} pathways in smooth muscle plasmalemma. *Journal of Membrane Biology* 1981; **59**: 19–25.
21. Toda N. Potentiation by ouabaine of the response to vasoconstrictor agents of isolated dog cerebral and mesenteric arteries soaked in Ca^{++}-free media. *Journal of Cardiovascular Pharmacology* 1982; **4**: 469–474.
22. Su JY. Mechanisms of action of isoflurane on contraction of rabbit conduit artery. *Anesthesia and Analgesia* 1996; **82**: 837–842.
23. Tsuchida H, Namba H, Seki S, Fujita S, Tanaka S, Namiki A. Role of intracellular Ca^{2+} pools in the effects of halothane and isoflurane on vascular smooth muscle contraction. *Anesthesia and Analgesia* 1994; **78**: 1067–1076.
24. Akata T, Boyle WA III. Dual actions of halothane on intracellular calcium stores of vascular smooth muscle. *Anesthesiology* 1996; **84**: 580–595.
25. Namba H, Tsuchida H. Effect of volatile anesthetics with and without verapamil on intracellular activity in vascular smooth muscle. *Anesthesiology* 1996; **84**: 1465–1474.
26. Tsuchida H, Namba H, Yamakage M, Fujita S, Notsuki E, Namiki A. Effects of halothane and isoflurane on cytosolic calcium ion concentrations and contraction in the vascular smooth muscle of the rat aorta. *Anesthesiology* 1993; **78**. 531–540.
27. Akata T, Boyle WA III. Volatile anesthetic actions on contractile proteins in membrane-permeabilized small mesenteric arteries. *Anesthesiology* 1995; **82**: 700–712.
28. Warner DO, Jones KA, Lorenz RR. The effects of halothane pretreatment on manganese influx induced by muscarinic stimulation of airway smooth muscle. *Anesthesia and Analgesia* 1997; **84**: 1366–1371.
29. Sill JC, Uhl C, Eskuri S, Van Dyke R, Tarara J. Halothane inhibits agonist-induced inositol phosphate and Ca^{2+} signaling in A7r5 cultured vascular smooth muscle cells. *Molecular Pharmacology* 1991; **40**: 1006–1013.
30. Sill JC, Eskuri S, Nelson R, Tarara J, Van Dyke RA. The volatile anesthetic isoflurane attenuates Ca^{++} mobilization in cultured vascular smooth muscle cells. *Journal of Pharmacology and Experimental Therapeutics* 1993; **265**: 74–80.
31. Fujihara H, Fukuda S, Fujihara N, Shimoji K. The effects of halothane on arginine-vasopressin-induced Ca^{2+} mobilization from the intracellular stores and the receptor-mediated Ca^{2+} entry from the extracellular space in single cultured smooth muscle cells of rat aorta. *Anesthesia and Analgesia* 1996; **83**: 584–590.
32. Marks TN, Dubyak GR, Jones SW. Calcium currents in the A7r5 smooth muscle-derived cell line. *Pflügers Archiv European Journal of Physiology* 1990; **417**: 433–439.
33. Iaizzo PA. The effects of halothane and isoflurane on intracellular Ca^{2+} regulation in cultured cells with characteristics of vascular smooth muscle. *Cell Calcium* 1992; **13**: 513–520.
34. Benham CD, Tsien RW. A novel receptor-operated Ca^{2+}-permeable channel activated by ATP in smooth muscle. *Nature (London)* 1987; **328**: 275–278.
35. Amédée T, Benham CD, Bolton TB, Byrne NG, Large WA. Potassium, chloride and non-selective cation conductances opened by noradrenaline in rabbit ear artery cells. *Journal of Physiology (London)* 1990; **423**: 551–568.
36. Enoki T, Miwa S, Sakamoto A, Minowa T, Komuro T, Kobayashi S, Ninomiya H, Masaki T. Long-lasting activation of cation current by low concentration of endothelin-1 in mouse fibroblasts and smooth muscle cells of rabbit aorta. *British Journal of Pharmacology* 1995; **115**: 479–485.
37. Pacaud P, Loirand G, Gregoire G, Mironneau C, Mironneau J. Noradrenaline- activated heparin-sensitive Ca^{2+} entry after depletion of intracellular Ca^{2+} store in portal vein smooth muscle cells. *Journal of Biological Chemistry* 1993; **268**: 3866–3872.
38. Byron K, Taylor CW. Vasopressin stimulation of Ca^{2+} mobilization, two bivalent cation entry pathways and Ca^{2+} efflux in A7r5 rat smooth muscle cells. *Journal of Physiology (London)* 1995; **485**: 455–468.

British Journal of Anaesthesia 1998; 81: 584–589

Antioxidant effects of propofol in human hepatic microsomes: concentration effects and clinical relevance

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Summary

Propofol is known to possess antioxidant properties. There is controversy regarding the mechanisms by which the drug produces its antioxidant effects and the significance of these effects in relation to plasma concentrations of propofol in clinical practice. We studied the effects of increasing concentrations of Intralipid, propofol, butylated hydroxytoluene (BHT) and a vitamin E analogue (Trolox C) in 0.9% saline on non-enzymic and enzymic lipid peroxidation in human hepatic microsomes, and on concentrations of antioxidant enzymes in a Hep G2 cell line. Propofol showed significant inhibition of lipid peroxidation, but was less potent than BHT or Trolox C. IC$_{50}$ values for non-enzymic and enzymic lipid peroxidation were mean 9.47 (SD 0.86) and 7.39 (0.84) µmol litre^{-1} for propofol, 1.30 (0.57) and 0.32 (0.02) µmol litre^{-1} for BHT and 2.34 (0.68) and 0.35 (0.04) µmol litre^{-1} for Trolox C, respectively. The antioxidant activities of propofol were substantially retained in the presence of up to 30 g litre^{-1} of human serum albumin. Propofol at concentrations of up to 100 µmol litre^{-1} had no significant effect on the activities of antioxidant enzymes. Clinically relevant concentrations of propofol produced significant inhibition of both enzymic and non-enzymic lipid peroxidation in hepatic microsomal preparations, possibly as a result of accumulation in lipophilic environments. Measurement of antioxidant effects of drugs in aqueous media may have little relevance to their effects in protecting against lipid peroxidation in biological systems. (*Br. J. Anaesth.* 1998; **81**: 584–589).

Keywords: anaesthetics i.v., propofol; enzymes, glutathione; liver, hepatocytes

Oxidant-mediated injury is thought to play an important role in several areas of critical illness, including ischaemia reperfusion injury (IRI)[1] and secondary neuronal injury after a variety of neurological insults. Several studies have demonstrated a benefit from the use of novel 21-aminosteroid compounds in animal models of focal ischaemia,[2–4] global ischaemia[5–7] or concussive brain injury.[8 9] These results support the investigation of other antioxidant compounds with potential neuroprotective properties.

Our previous work demonstrated that propofol (Diprivan) had antioxidant properties *in vitro*,[10] and was more effective than other i.v. anaesthetic agents at reducing the abnormalities in ion fluxes produced during cerebral ischaemia in a cat model.[11] We have also shown that propofol had acute neuroprotection in a rodent model of IRI, to an extent that cannot be accounted for by reduction of cerebral oxygen use.[12] The possibility that these neuroprotective effects of propofol are caused by its antioxidant properties is supported by the increased resistance to oxidant injury in red blood cells[13] and in hepatic microsomes obtained from rats anaesthetized with propofol.[14]

Confirmation of a clinically useful effect depends on demonstration that propofol has antioxidant properties at concentrations achieved during clinical anaesthesia. *In vitro* studies that have addressed this issue are conflicting. Eriksson, Pollesello and Saris[15] demonstrated that propofol protected rat liver mitochondria against lipid peroxidation and Musacchio and colleagues[16] showed that propofol produced significant protection against lipid peroxidation in rat liver mitochondria and microsomes, and in rat brain synaptosomes, with median inhibitory concentrations (IC$_{50}$) of 1.1–26.4 µmol litre^{-1}, which is similar to the clinical anaesthetic concentration range,[17] whereas IC$_{50}$ values for the established free radical scavenger butylated hydroxytoluene (BHT) were 1.6–33 µmol litre^{-1}. However, Green, Bennet and Nelson studied the antioxidant effects of propofol in an aqueous *in vitro* system and found little evidence of antioxidant activity at concentrations less than 60 µmol litre^{-1} in a variety of oxidant reactions.[18] Neither of these groups compared propofol with other clinically relevant naturally occurring antioxidant compounds such as vitamin E. Aarts and colleagues showed that propofol protected a-tocopherol-depleted rat hepatic microsomes against oxidant damage,[19] but did not study the effects of BHT, and therefore comparison with earlier studies was not possible.

We have studied the antioxidant effects of propofol for several reasons. First, we compared the antioxidant effects of propofol with those of BHT so that comparison with previous studies was possible, and with Trolox C (the water-soluble analogue of vitamin

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E) so that we could compare propofol with a clinically relevant antioxidant compound. Second, we compared these compounds in a preparation of human liver microsomes to exclude effects that might arise from inter-species differences. Finally, we wished to delineate specific processes affected by propofol. Consequently, we studied the effects on both non-enzymic and enzymic lipid peroxidation, and since many redox antioxidants modulate the production of intrinsic antioxidant enzymes[20] *in vivo* via interaction with an antioxidant responsive element (ARE) at transcription sites,[21] we studied the effect of these compounds on antioxidant enzymes in a Hep G-2 hepatoma cell line.

Materials and methods

Appropriate institutional procedures were followed, but formal Ethics Committee approval was not required as tissues obtained for these studies were from donor liver that would have been discarded at the end of a "cut down" procedure at orthotopic liver transplantation.

HUMAN HEPATIC MICROSOME PREPARATION

Hepatic tissues for microsome preparations were from healthy human livers obtained at the time of liver transplantation and stored at −70°C. Tissues were available as a result of "cut down" procedures on large donor organs being transplanted to paediatric recipients. Data reported are from liver tissues obtained from three separate donors. Microsomes were prepared freshly by the method of Lambert,[22] using a buffer of BisTris propane 20 mmol litre^{-1} (pH 7.0)–sucrose 0.25 mol litre^{-1}–KCl 0.15 mmol litre^{-1}. Microsomes were washed with Tris/HCl 150 mmol litre^{-1}, pH 8.0, to remove extraneous cytosolic proteins. The amounts of lactate dehydrogenase and glutamate dehydrogenase in the samples showed that the vesicles were free from cytosolic and mitochondrial contamination, respectively, and the amount of acid phosphatase showed that lysosomal contamination was minimal.[22 23] All assays were in triplicate, performed on microsomes from the same liver, and results shown are mean (SD) for each concentration, indexed where appropriate to lipid peroxidation in the absence of any agent in each series of experiments.

DETERMINATION OF PROTEIN CONCENTRATION IN MICROSOMAL PREPARATIONS

Microsomal protein concentrations were determined by the bicinchonic acid method,[24] using bovine serum albumin as standard.

ASCORBATE–FE(III)-INDUCED PEROXIDATION

Microsomes (equivalent to 0.4 mg of liver microsomal protein) were suspended in KCl 150 mmol litre^{-1} containing $FeCl_3$ 0.2 mmol litre^{-1} (freshly prepared in water) and various amounts of test material. Peroxidation was initiated by addition of ascorbate (to a final concentration of 0.05 mmol litre^{-1}), in a final volume of 0.4 ml. Samples were incubated at 37°C for 40 min, and the reactions terminated by addition of 0.8 ml of 20% w/v trichloroacetic acid–0.4% thiobarbituric acid–HCl 0.25 mol litre^{-1} and 0.01 ml of butylated hydroxytoluene (5%) in ethanol. Thiobarbituric acid reactive substances (TBARS) were measured after incubation at 80°C for 15 min.[25] The concentration of the indicator reaction product (malondialdehyde) was measured as the optical density at 535 nm, and converted into micromoles using an extinction coefficient of 1.56×10^5 mol litre^{-1} cm^{-1}, as described by Wills.[26] Test substances alone showed no significant reaction in the TBARS assay.

NADPH–IRON-INDUCED PEROXIDATION

Liver microsomes (equivalent to 0.4 mg of microsomal protein) were suspended in BisTris propane buffer 20 mmol litre^{-1}, pH 7.0, and the following added in sequence to the final concentration indicated: KCl 150 mmol litre^{-1}; ADP 0.8 mmol litre^{-1}; $FeCl_3$ 0.2 mmol litre^{-1} (freshly prepared in water) and test sample. Peroxidation was initiated with NADPH (final concentration 0.4 mmol litre^{-1}) in a total volume of 0.4 ml. Samples were incubated and processed as described above.

CALCULATION OF IC_{50} VALUES

Concentrations of test substance required to produce 50% inhibition of a reaction (IC_{50} values) were calculated by fitting a third-order polynomial curve to the data. The derived IC_{50} values are shown in the text and tables together with SD of the estimate.

EFFECT OF ALBUMIN ON ANTIOXIDANT EFFECTS OF PROPOFOL

In view of the fact that propofol is extensively protein bound, the antioxidant effects of propofol on ascorbate–Fe(III)-induced lipid peroxidation and NADPH–iron-induced peroxidation were assessed in the presence of human serum albumin 0.1, 1.0, 10 and 30 g litre^{-1}. As albumin may have independent antioxidant effects, the effect of each test concentration of albumin on peroxidation was also measured in experiments where no propofol was added.

HUMAN HEP G2 HEPATOMA CELL CULTURE

Hep G2 cells were grown routinely in Eagle's minimal essential medium with L-glutamine, non-essential amino acids and 10% fetal calf serum at 37°C in 5% carbon dioxide in air. Confluent monolayers of cells were treated with a variety of concentrations of propofol for 24 h, after which cells were harvested using trypsin–EDTA.[27] Cytosolic extracts of these cells were obtained by sonication in 0.1% digitonin in Tris-HCl 0.1 mol litre^{-1} pH 7.4, DTT 1 mmol litre^{-1} and phenylmethylsulphonyl fluoride 1 mmol litre^{-1}. The supernatants (16 000 g, 30 min) were used for enzymatic assays. Phospholipid hydroperoxide glutathione peroxidase (PHGPx) activity was measured by HPLC assay using 1-palmitoyl-2-(13-hydroperoxy-*cic9*, *trans*-11-octadecadienoyl)-L-3-phosphatidylcholine as substrate.[28] Glutathione peroxidase (GPX) activity was measured using hydrogen peroxide as substrate.[29] Glutathione S-transferase (GST) activity was measured using 1-chloro-2,4-dinitrobenzene (CDNB).[30] Protein contents of the cell extracts were determined using the dye binding assay (Bio-Rad) protein assay reagent using bovine serum albumin as standard.

TEST SUBSTANCES

Diprivan (1% propofol in 10% soybean oil emulsified with egg phosphatide; Zeneca, Macclesfield, UK) was diluted to appropriate concentrations in 0.9% saline for all studies in which propofol was used. Control studies were performed with 10% Intralipid (emulsified soybean oil and egg phosphatide; Kabi Pharmacia, UK). Trolox C and BHT were obtained from Sigma Chemicals, UK.

Results

Intralipid had no effect on non-enzymic or enzymic lipid peroxidation in concentrations that corresponded to the amounts of Intralipid present in Diprivan solutions (results not shown). Figure 1 shows the effects of increasing concentrations of propofol, BHT and Trolox on peroxidation of human liver microsomes induced by ascorbate–Fe(III) (fig. 1) or NADPH–Fe(III) (fig. 2). Propofol showed similar inhibition curves in both assays with IC_{50} values of 9.5 and 7.4 μmol litre^{-1} in the aqueous phase, respectively. Clearly, propofol was equally effective at prevention of peroxidation in both enzymic and non-enzymic systems. The relative effectiveness of propofol compared with BHT and Trolox in these assays is shown in table 1 and figures 1 and 2.

In separate experiments, we found that there was no reduction in the antioxidant activity of propofol when experiments were repeated with albumin 0.1, 1.0 and 10.0 g litre^{-1} in the medium (results not shown). Data from experiments where albumin 30 g litre^{-1} was used were complicated by the fact that this concentration of albumin resulted in 40% reduction in ascorbate–Fe(III)-induced peroxidation and

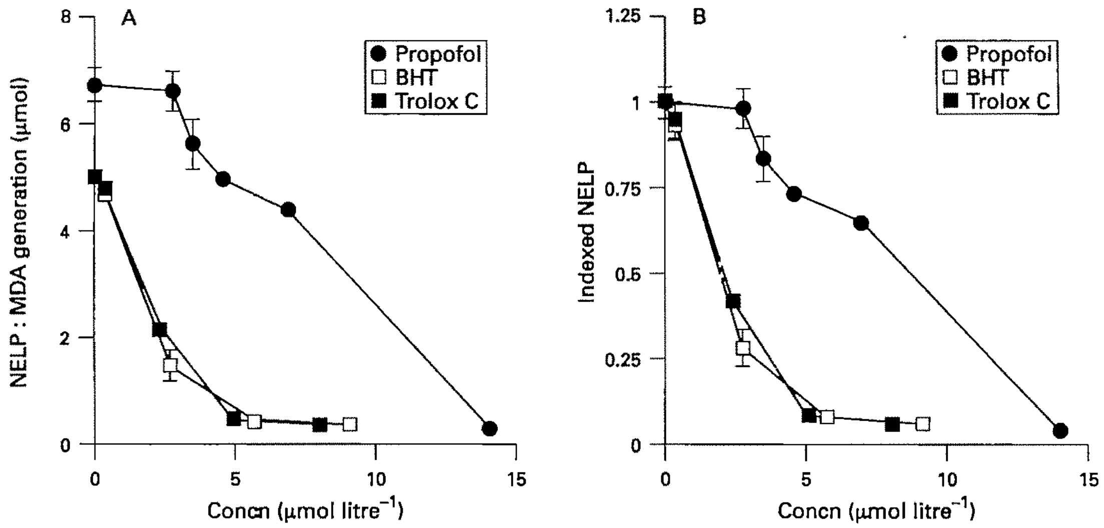

Figure 1 Concentrations of propofol, BHT and Trolox C *vs* extent of inhibition of non-enzymic lipid peroxidation (NELP) in a human liver microsome preparation, presented as (A) measured generation of malondialdehyde (MDA) in individual experiments, and (B) with all values indexed to the level of lipid peroxidation measured in the absence of any antioxidant compound in each set of experiments. Data are mean (SD).

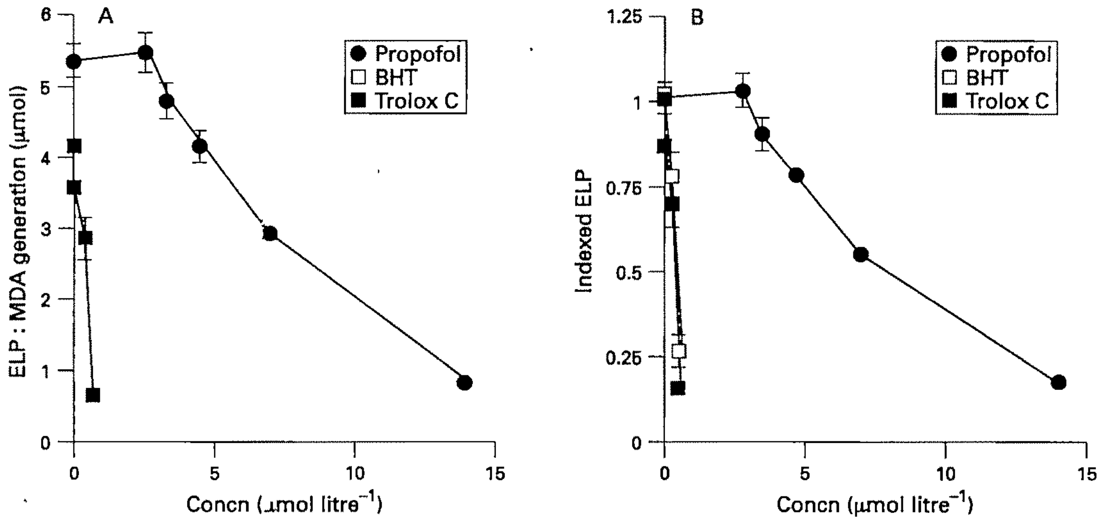

Figure 2 Concentrations of propofol, BHT and Trolox C *vs* extent of inhibition of enzymic lipid peroxidation (ELP) in a human liver microsome preparation, presented as (A) measured generation of malondialdehyde (MDA) in individual experiments, and (B) with all values indexed to the level of lipid peroxidation measured in the absence of any antioxidant compound in each set of experiments. Data are mean (SD).

Table 1 IC50 values for propofol, BHT and Trolox C for inhibition of lipid peroxidation in normal human liver microsomes (mean (sd))

Agent	IC50 for non-enzymic lipid peroxidation (μmol litre–1)	IC_{50} for enzymic lipid peroxidation (μmol litre–1)
Propofol	9.47 (0.86)	7.39 (0.84)
BHT	2.34 (0.68)	0.35 (0.04)
Trolox C	1.30 (0.57)	0.32 (0.02)

Table 2 Effect of propofol on antioxidant enzyme activity in a Hep G2 cell line (mean (sd)). PHGPx=phospholipid hydroperoxide glutathione peroxidase; GPX=glutathione peroxidase; and GST=glutathione S-transferase

Propofol concn (μmol litre–1)	Antioxidant enzyme activity (n=4) (nmol of substrate min–1 mg protein–1)		
	PHGPx	GPX	GST
0	2.40 (0.17)	5.37 (0.57)	25.6 (2.7)
1	2.48 (0.20)	6.00 (0.26)	25.8 (1.5)
10	2.44 (0.14)	6.00 (0.40)	22.1 (1.7)
100	2.44 (0.25)	4.87 (0.51)	21.6 (1.7)

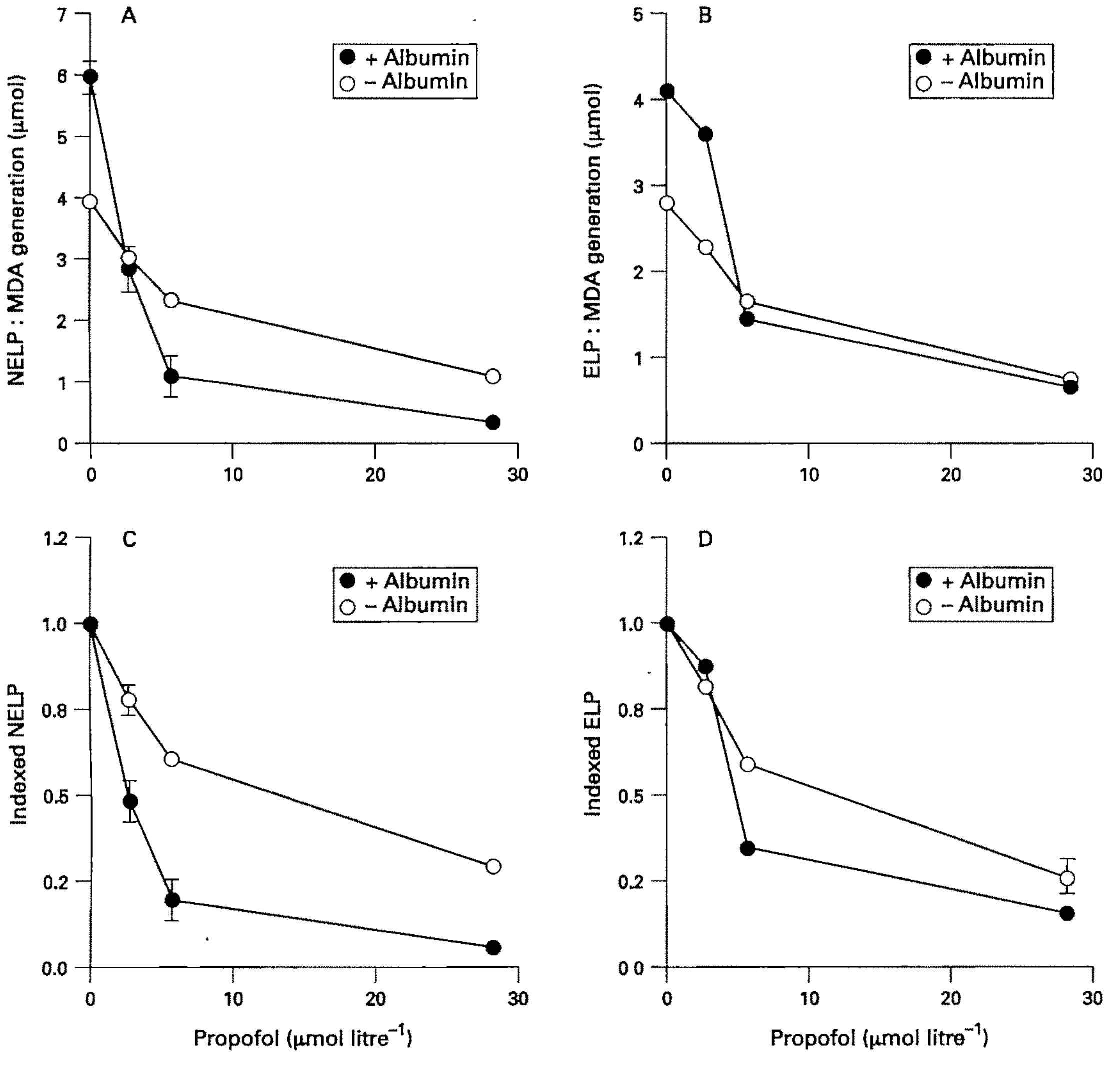

Figure 3 Propofol-induced inhibition of lipid peroxidation in the presence (+) and absence (–) of human serum albumin 30 g litre^{-1}. The curves on the left (A, C) are for ascorbate–Fe(III)-induced (non-enzymic) lipid peroxidation (NELP), and those on the right (B, D) are for NADPH–iron-induced (enzymic) lipid peroxidation (ELP). The two upper curves (A, B) show the actual concentrations of lipid peroxidation, measured by generation of malondialdehyde (MDA), while the two lower curves (C, D) show the same data with values indexed to initial measurements in the absence of propofol in each set of experiments. Note that addition of albumin results in a 40% reduction in lipid peroxidation. Residual peroxidation is effectively inhibited by propofol, albeit with a change in IC_{50}. Data are mean (SD).

NADPH–iron-induced lipid peroxidation. However, the residual peroxidation reaction was effectively inhibited by propofol (fig. 3), with IC_{50} values of 9.54 (0.02) and 12.43 (0.41) μmol litre^{-1} (*vs* 1.74 (0.39) and 5.54 (0.59) μmol litre^{-1} in the absence of albumin), respectively.

The effect of propofol on the activity of key antioxidant and detoxifying enzymes in Hep G2 cell lines is shown in table 2. There were no significant changes with propofol for all concentration ranges.

Discussion

We have shown that clinically relevant concentrations of propofol inhibited both enzymic and non-enzymic lipid peroxidation, suggesting that it does so via mechanisms independent of cytochrome P450. Previous studies have reported that propofol inhibits microsomal cytochrome P450 activity. However, the IC_{50} values for this effect are considerably higher than the typical clinical concentrations (<30 μmol litre^{-1}) that we chose to examine in our studies. Thus Baker, Chadam and Ronnenberg[31] showed an IC_{50} value of approximately 350 μmol litre^{-1} in rat hepatic microsomes, Janicki, James and Erskine[32] showed an IC_{50} of approximately 60–100 μmol litre^{-1} in human hepatic microsomes and Chen and colleagues[33] showed an IC_{50} of 300–1000 μmol litre^{-1} in human liver microsomes. Lower IC_{50} values of 25–30 μmol litre^{-1} were reported by Baker, Chadam and Ronnenberg,[31] but these were in hepatic microsomes obtained from phenobarbital treated rats. In contrast, Chen and colleagues[33] showed that doses as high as 100 mg kg^{-1} i.p., twice daily for 2 weeks, failed to produce significant effects on cytochrome P450 activity. However, we cannot exclude the possibility that the antioxidant effects we observed were related in part to inhibition of NADPH cytochrome P450 reductase, although there are no data in the literature to support such an effect either for propofol or for other closely related phenolic compounds.

The IC_{50} for propofol in both enzymic and non-enzymic lipid peroxidation reactions was 7–9 μmol litre^{-1}. These results agree with those of Musacchio and colleagues,[16] who found an IC_{50} of 1–25 μmol litre^{-1}, and Aarts and colleagues[19] who demonstrated significant antioxidant protection by propofol at concentrations of 11.2 and 28 μmol litre^{-1}. We found that both BHT and Trolox C were more potent antioxidants than propofol. The IC_{50} values for enzymic and non-enzymic lipid peroxidation were 0.35 and 2.3 μmol litre^{-1}, respectively, for BHT, and 0.32 and 1.3 μmol litre^{-1}, respectively, for Trolox C. Our comparative data for BHT and propofol differed from those observed by Musacchio and colleagues,[16] who demonstrated similar antioxidant potencies for the two compounds in their assay. These differences may be related to species (rat *vs* human hepatocytes) or to differences in experimental methods.

These findings need to be assessed in the context of plasma concentrations achieved in clinical practice. Typical plasma concentrations of propofol during anaesthesia are 2.8–28 μmol litre^{-1} which are similar to the concentrations that inhibited lipid peroxidation in our studies. While comparison with clinically relevant concentrations of α-tocopherol (approximately 33 μmol litre^{-1})[34] would have been interesting, its lack of solubility in water made direct comparison in our experiments difficult.

Consideration of lipid solubility and partitioning is important with reference to propofol, which is a highly lipid soluble compound with a log octanol/water partition coefficient of 3.7, and estimates of its relative concentration in lipid membranes (compared with the aqueous environment) vary from 4 to 200 (data from Zeneca, Macclesfield, UK). This fact may help to explain the discrepancy between data from Green, Bennet and Nelson[18] and the results obtained by Musacchio and colleagues,[16] Eriksson, Pollesello and Saris,[15] Aarts and colleagues[19] and ourselves. Green, Bennet and Nelson[18] studied the antioxidant effects of propofol in an aqueous system, which may not have been relevant to an agent that prevents lipid peroxidation. The relative concentration of propofol in lipid membranes may explain its antioxidant activity in microsomal preparations in the latter three studies.

Propofol is highly protein bound, and the presence of albumin in the medium may be expected to result in significant binding and reduction in antioxidant activity. However, while human serum albumin 30 g litre^{-1} resulted in some decrease in the potency of propofol for inhibition of both types of peroxidation reactions, IC_{50} values were well within the range of plasma concentrations observed during clinical use of the agent. IC_{50} values for propofol in the absence of albumin in these experiments were different from those obtained in experiments that compared propofol with BHT and Trolox C. However, these two sets of studies were performed on different liver samples, and the experiments were separated by several months, as timing of these experiments was dictated by the availability of cut down livers. In this context the observed differences are not excessive.

Propofol had no significant effects on the activities of antioxidant enzymes in the Hep G2 cell line, although there appeared to be a trend towards reducing activities of GST and GPX at high propofol concentrations (approximately 100 μmol litre^{-1}). These enzymes are known to be induced in Hep G2 cells by antioxidant compounds such as picolines[35] and *in vivo* by extracts of cruciferous vegetables.[36 37] These findings also distinguish propofol from other structurally similar phenolic antioxidant compounds such as BHT, which undergo redox cycling and tend to increase concentrations of these enzymes.[20] Consequently, administration of propofol is unlikely to be associated with antioxidant effects that persist beyond the duration of exposure to the drug. Further investigations are required to clarify if prolonged exposure to high concentrations of propofol can result in attenuation of the intrinsic cellular antioxidant defences, with an increase in vulnerability to oxidant attack after withdrawal of the agent.

In summary, we conclude that propofol exhibits useful antioxidant activities in lipid membranes when concentrations in the aqueous environment are well within the anaesthetic dose range, probably as a result of preferential partitioning into hydrophobic environments. This finding may be relevant in the context of clinical use of propofol as an antioxidant, as it may be able to inhibit or limit lipid peroxidation in cell membranes. Maximal inhibition of lipid peroxidation was achieved in our experiments at concentrations <30 μmol litre^{-1}, and there may be unfavourable effects on cellular antioxidant enzyme levels at concentrations above the clinical range, with additional effects on cytochrome P450 becoming apparent. Optimal concentrations of propofol for antioxidant activity appear to coincide with plasma concentrations obtained during clinical anaesthesia, and these effects are seen at clinically relevant concentrations of propofol, even in the presence of physiological concentrations of human serum albumin.

Acknowledgement

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References

1. Traystman RJ, Kirsch JR, Koehler RC. Oxygen radical mechanisms of brain injury following ischaemia and reperfusion. *Journal of Applied Physiology* 1991; 71: 1185–1195.
2. Xue D, Slivka A, Buchan AM. Tirilazad reduces cortical

infarction after transient but not permanent focal cerebral ischemia in rats. *Stroke* 1992; **23**: 894–899.

3. Haraldseth O, Gronas T, Unsgard G. Quick metabolic recovery after forebrain ischemia in rats treated with the antioxidant U74006F. *Stroke* 1992; **22**: 1188–1192.
4. Hall ED, Pazara KE, Braughler JM. Effects of tirilazad mesylate on postischemic lipid peroxidation and recovery of extracellular ischemia in gerbils. *Stroke* 1991; **22**: 361–366.
5. Natale JE, Schott RJ, Hall Ed, Braughler JM, Dalecy LG. The 21-aminosteroid U74006 reduces systemic lipid peroxidation, improves neurological function, and reduces mortality after cardiopulmonary arrest in dogs. *Progress in Clinical and Biological Research* 1989; **308**: 891–896.
6. Hall ED, Yonkers PA. Attenuation of postischemic cerebral hypoperfusion by the 21-aminosteroid U74006F. *Stroke* 1988; **19**: 340–344.
7. Perkins WJ, Milde LN, Milde JH, Michenfelder JD. Pretreatment with U74006F improves neurological outcome following complete cerebral ischemia in dogs. *Stroke* 1991; **22**: 902–909.
8. McIntosh TK, Banbury M, Smith D, Thomas M. The novel 21-aminosteroid U-74006F attenuates cerebral oedema and improves survival after brain injury in the rat. *Acta Neurochirugica Supplement (Wien)* 1990; **51**: 329–330.
9. Hall ED, Yonkers PA, McCall JM, Braughler JM. Effects of the 21-aminosteroid U74006F on experimental head injury in mice. *Journal of Neurosurgery* 1988; **68**: 456–461.
10. Murphy PG, Myers DS, Davies MJ, Davies M, Webster N, Jones JG. The anti-oxidant potential of propofol (2,6-diisopropylphenol). *British Journal of Anaesthesia* 1992; **68**: 613–618.
11. Weir DL, Goodchild CS, Graham DI. Propofol: effects on indices of cerebral ischemia. *Journal of Neurosurgical Anesthesiology* 1989; **1**: 284–289.
12. Young Y, Tisavipat N, Pickard JD, Jones JG, Menon DK. Neuroprotection in experimental temporary focal cerebral ischaemia: propofol versus isoflurane. *European Journal of Anaesthesiology* 1997; **14**: 320–326.
13. Murphy PG, Atkinson R, Columb MO, Myers DS, Day P. Effect of propofol and thiopentone on free radical-induced haemolysis. *British Journal of Anaesthesia* 1992; **69**: 532P–533P.
14. Murphy PG, Bennet JR, Myers DS, Davies MJ, Jones JG. The effect of propofol anaesthesia on free radical-induced lipid peroxidation in rat liver microsomes. *European Journal of Anaesthesiology* 1993; **10**: 261–266.
15. Eriksson O, Pollesello P, Saris NEL. The inhibition of lipid peroxidation in rat liver mitochondria by the general anesthetic propofol. *Biochemical Pharmacology* 1992; **44**: 391–393.
16. Musacchio E, Rizzoli V, Bianchi M, Bindoli A, Galzigna L. Antioxidant action of propofol on liver microsomes, mitochondria and brain synaptosomes in the rat. *Pharmacological Toxicology* 1991; **69**: 75–77.
17. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesthesia and Analgesia* 1987; **66**: 1256–1263.
18. Green TR, Bennet SR, Nelson VM. Specificity and properties of propofol as an antioxidant free radical scavenger. *Toxicology Applied Pharmacology* 1994; **129**: 163–169.
19. Aarts L, van der Hee R, Dekker I, de Jong J, Langmeijer H, Bast A. The widely used anesthetic agent propofol can replace a-tocopherol as an antioxidant. *FEBS Letters* 1995; **357**: 83–85.
20. Rushmore TH, Morton MR, Pickett CB. The antioxidant responsive element. Activation by oxidative stress and identification of the DNA consensus sequence required for functional activity. *Journal of Biological Chemistry* 1991; **266**: 11632–11639.
21. Meyer M, Schreck R, Baeuerle PA. H_2O_2 and antioxidants have opposite effects on activation of NF—B and AP-1 in intact cells: AP-1 as secondary antioxidant-responsive factor. *EMBO Journal* 1993; **12**: 2005–2015.
22. Lambert N. Isolation of microsomes. In: Harris ELV, Angel S, eds. *Protein Purification Methods: A Practical Approach*. Oxford: IRL Press, 1989; 101–108.
23. Lambert N, Chambers SJ, Plumb GW, Williamson G. Human cytochrome P-450s are pro-oxidants in iron/ascorbate-initiated lipid peroxidation. *Free Radical Research* 1996; **24**: 177–185.
24. Smith PK, Krohn RI, Hermanson GT, Mallia AK, Gartner FH, Provenzano MD, Fujimoto EK, Goeke NM, Olson BJ, Klenk DC. Measurement of protein using bicinchoninic acid. *Analytical Biochemistry* 1985; **150**: 76–85.
25. Buege JA, Aust SD Microsomal lipid peroxidation. *Methods in Enzymology* 1978; **30**: 302–310.
26. Wills ED. Lipid peroxide formation in microsomes. General considerations. *Biochemical Journal* 1969; **113**: 315–324.
27. Belisario MA, Arena AR, Pecce R, Borgia R, Staiano N, Lorenzo FD. Effect of enzyme inducers on metabolism of 1-nitropyrene in human hepatoma cell line Hep G2. *Chemical–Biological Interactions* 1991; **78**: 253–268.
28. Bao YP, Chambers SJ, Williamson D. Direct separation of hydroperoxy- and hydroxy-phosphatidylcholine derivatives· application to the assay of phospholipid hydroperoxide glutathione peroxidase. *Analytical Biochemistry* 1995; **224**. 395–399.
29. Wendel A. Glutathione peroxidase. *Methods in Enzymology* 1981; **77**: 325–333.
30. Habig W, Jakoby W. Assays for differentiation of glutathione S-transferase. *Methods in Enzymology* 1981; **77**. 398–405.
31. Baker MT, Chadam MV, Ronnenberg WC. Inhibitory effects of propofol on cytochrome P450 activities in rat hepatic microsomes. *Anesthesia and Analgesia* 1993; **76**. 817–821.
32. Janicki PK, James MFM, Erskine WAR. Propofol inhibits enzymatic degradation of alfentanil and sufentanil by isolated liver microsomes *in vitro*. *British Journal of Anaesthesia* 1992; **68**: 311–312.
33. Chen TL, Ueng TH, Chen SH, Lee PH, Fan SZ, Liu CC. Human cytochrome P450 mono-oxygenase system is suppressed by propofol. *British Journal of Anaesthesia* 1995; **74**: 558–562.
34. Stephens NG, Parsons N, Schofield PM, Kelly F, Cheesman K, Mitchinson MJ, Brown MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* 1996; **347**: 781–786.
35. Dierickx PJ. The influence of picolines on glutathione transferase activity and subunit composition in human liver derived Hep G2 cells. *Biochemical Pharmacology* 1994; **48**: 1976–1978.
36. Williamson G, DuPont MS, Wanigatunga S, Heaney RK, Musk SRR, Fenwick GR, Rhodes MJC. Induction of glutathione S-transferase activity in Hep G2 cells by extracts of fruits and vegetables *Food Chemistry* 1997; **60**: 157–160.
37. Bao Y-P, Williamson G. Phospholipid hydroperoxide glutathione peroxidase, a selenoenzyme, protects against free-radical-mediated damage to Hep G2 cells. In: Packer L, Traber MG, Xin W, eds. *Proceedings of the International Symposium on Natural Antioxidants: Molecular Mechanisms and Health Effects.* Champaign, Illinois: AOCS Press 1996; 661–664.

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REVIEW ARTICLE

Continuous spinal anaesthesia

N. M. DENNY AND D. E. SELANDER

Continuous spinal anaesthesia (CSA) is the technique of producing and maintaining spinal anaesthesia with small doses of local anaesthetic which are injected intermittently into the subarachnoid space via an indwelling catheter. The concept was described first in 1907 by Dean,[11] a British surgeon, who wrote of placing a needle in the subarachnoid space and leaving it *in situ* so that repeated doses of local anaesthetic could be injected. In 1939, Lemmon described a malleable needle which could be left in the subarachnoid space allowing intermittent injection of local anaesthetic via a rubber tube.[37] The catheter technique was described first by Edward Tuohy in 1944.[71] He described CSA as a safe and versatile technique without significant problems of post-dural puncture headache (PDPH).

In the early 1950s, Dripps reported a high incidence of paraesthesia and low success rates with CSA, and this led to a decline in its use.[18] Fears that CSA would result in a higher incidence of PDPH and neurological complications, together with the development of the continuous epidural anaesthetic technique,[10] further discouraged the use of CSA.

When CSA was reintroduced in the mid 1980s, the advantages described were: excellent control of segmental spread and duration; effectiveness of small doses of local anaesthetic; and decreased risk of cardiovascular side effects.[15] The incidence of PDPH also seemed low, especially in elderly patients.[15 40]

During the late 1980s, microcatheters were developed to make the CSA technique suitable for use in young patients without incurring an unacceptable risk of PDPH.[28] However, not only was it difficult to show a decreased frequency of PDPH, but serious neurological complications were reported after the use of spinal microcatheters and high concentration, hyperbaric local anaesthetics.[56] As a consequence, in 1992 the Food and Drug Administration (FDA) of the USA banned the use of spinal catheters thinner than 24-gauge,[20] and the manufacturers of local anaesthetics declared that their drugs were not indicated for use with CSA.[16] This reinforced the misconception that CSA was a dangerous technique.

However, our experience is that CSA is a valuable and safe technique when performed correctly. The purpose of this article is to review the relevant aspects of CSA, its indications and side effects, and to comment on drugs, equipment and technique.

History and experience with large-bore catheters

As we know it today, CSA was first described by Edward Tuohy in 1944. He devised a technique of inserting a ureteral catheter 4–5 cm into the subarachnoid space via a 15-gauge Huber point needle and initiating spinal anaesthesia with incremental doses of local anaesthetic. He found that the dose of local anaesthetic used for single injection spinal anaesthesia could be reduced by 20–25% with the CSA technique.[71 72] He recommended it for surgery below the umbilicus and reported no increase in the incidence of PDPH compared with single injection techniques and no neurological complications. His comments on the technique are as revealing and pertinent today as they were then: "A question has been raised concerning the direction the catheter will advance in the subarachnoid space after the tip of the catheter leaves the end of the guiding needle. The direction cannot be predicted positively, but if the tip of the catheter is bent slightly before introducing it into the needle, I have found that the catheter will advance *cephalad* (our italics) in most cases. This has been determined and verified by using leaded ureteral catheters which are opaque radiographically. If the catheter turns *caudad* (our italics) on entering the subarachnoid space, this fact can usually be surmised or detected shortly after the first dose of the spinal anesthetic agent has been introduced because of the *segmental distribution of the resulting anesthesia* (our italics). Under these circumstances it is suggested that the remaining amount of the anesthetic solution in the syringe be diluted with an equal volume of saline to make a 1.5% solution of procaine hydrochloride. Twice as much solution (volume) should then be injected when additional doses are required".[71]

In 1950, Dripps reviewed reports on single injection spinal anaesthesia (SSA) and CSA with a malleable needle and catheter techniques.[18] He found an 8% (43 of 506) incidence of failed anaesthesia with CSA compared with 1.9% (37 of 1921) with SSA. Also, he found more technical difficulties with the catheter technique and a significantly higher incidence of transient paraesthesiae (33%) than with single injection techniques (13%).[18] Over the next 25 yr, CSA was used little, as reflected by the paucity of references in the literature, and it is hard not to conclude that this was a direct result of Dripps' article.

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Keywords: anaesthetic techniques, subarachnoid; anaesthetics local; equipment, catheters subarachnoid

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In 1952, in a series of 600 poor-risk surgical patients (24% were younger than 60 yr of age) who had CSA using 16-gauge Huber point needles, Brown found a failure rate of only 2%, and a 14% incidence of transient paraesthesia on threading the catheter.[2] The PDPH rate was 9.8%, and there were four cases of extraspinal neuropathies (three sixth nerve palsies and one peroneal) which recovered spontaneously.

In 1972, Giuffrida and colleagues described the use of CSA for Caesarean section in 75 patients using 21-gauge Huber point needles and 24-gauge catheters.[22] There were no failures, PDPH was reported in 12 patients (16%) and there were no neurological complications. In the same year, Kallos and Smith reported no failures, no complications and no PDPH in a series of 121 patients who had CSA for hip surgery (table 1).[30] They used 20-gauge nylon epidural catheters which were inserted through 18-gauge Hustead or Tuohy needles.

In 1981, Rao and El-Etr investigated the incidence of neurological complications arising from anticoagulant therapy after epidural and subarachnoid catheterization in 3164 and 847 patients, respectively (catheter size was not specified). Twenty patients experienced minor complications, five of which were neurological (four after epidural, one after subarachnoid blocks), and 15 low back pain (nine epidural, six subarachnoid) which were self-limiting and resolved with time.[54] There was no incidence of peridural haematoma leading to spinal cord compression. There was no report on the incidence of PDPH.

In 1987, Denny and colleagues, in the first prospective study of PDPH after CSA, assessed 117 patients with a mean age of 63 yr and found only one patient, a 29-yr-old man, who developed PDPH.[15] They used 18-gauge Hustead Tuohy needles (which were inserted with the bevel parallel to the longitudinal fibres of the dura) with 20-gauge nylon epidural catheters inserted 2–4 cm into the subarachnoid space. Difficulty threading the catheter was experienced in five patients (4.3%) and there were six (5.1%) failures with the technique (which led to general anaesthesia), but no neurological sequelae. Denny and colleagues postulated, as an explanation for the unexpectedly low incidence of PDPH, that the spinal catheter, if left *in situ* long enough, might induce an inflammatory reaction around the puncture site, and "that when the catheter is removed, edema or fibrinous exudate resulting from the inflammatory reaction seals the hole in the dura, thus preventing leakage of cerebrospinal fluid (CSF)". It was concluded that "with a PDPH incidence of less than 1% and the possibility of safely controlling the level of anesthesia, continuous spinal anesthesia offers an excellent method for long operations, particularly in elderly or severely ill patients".[15]

Table 1 Incidence of post-dural puncture headache (PDPH) (retrospective studies). *All Caesarean section patients, **all obstetric patients

Study	No. patients	Age (yr)	Catheter (gauge)	PDPH (%)
Kallos[30]	121	59pts<60	20	0
Giuffrida[22]	75*	< 40	24	16
Peterson[50]	52	70	20	0
Mahisekar[40]	226	62	20	0
Horlocker[27]	474	63	20	3.4
Horlocker[27]	127**	29	28	33

A similar low incidence of PDPH was reported in 1991 by Mahisekar and colleagues in a retrospective series of 226 patients after CSA with 18-gauge Tuohy needles and 20-gauge catheters, performed from 1981 to 1985. They reported no other complications.[40]

The hypothesis proposed by Denny and colleagues that the prolonged presence of the spinal catheter may prevent PDPH was supported by a retrospective study by Cohen and co-workers, which showed that prolonged placement of large-bore catheters in obstetric patients after accidental dural puncture appeared to reduce the incidence of PDPH.[9] However, in a study of 87 patients, aged 40–90 yr, undergoing orthopaedic procedures with CSA, performed with 18-gauge Tuohy needles and 20-gauge nylon catheters, Liu and colleagues found that prolonged spinal catheterization did not reduce the incidence of PDPH (9.2%).[38]

In 1989, Sutter, Gamulin and Forster, in a retrospective series of 457 patients who had CSA using 20-gauge catheters, reported not only greater cardiovascular stability but a significantly lower failure rate (1.7%) than the 9% in 274 similar patients who received epidural anaesthesia. No infections or neurological complications were found, but the incidence of PDPH was not reported.[69]

In 1995, Van Gessel, Forster and Gamulin showed that it was feasible to use CSA in a teaching environment. They detected no incidence of PDPH after CSA with 20-gauge catheters in 100 patients aged more than 65 yr. They demonstrated that although the failure rate for their residents was 6%, the technique was 100% successful in experienced hands.[75]

In 1997, Horlocker and co-workers, in a retrospective series of 474 patients who had CSA with 20-gauge catheters, reported a low PDPH incidence (3.4%) and a failure rate of 3.4%.[27] However, one patient developed aseptic meningitis and another, a 76-yr-old, 109-kg female with a history of lumbar radiculopathy, developed a cauda equina-like syndrome (CES) after administration of 5% hyperbaric lidocaine (lignocaine) 120 mg.

In summary, experience of CSA using 20-gauge catheters in elderly patients shows that the technique is safe and easy to use. The major complication was PDPH, which varied from 0 to 9.2% (tables 1, 2), but with the exception of one case of CES with tetracaine[56] and one with 5% lidocaine,[27] there were no major neurological complications. The overall reported failure rate was 2.5%, which is similar to single injection techniques[15 27 40 46 69 70 75] (table 3).

Microcatheters

After publication of the prospective study by Denny and colleagues in 1987,[15] and the introduction of the microcatheter technique in 1990,[28] there was a resurgence in popularity of CSA with both large-bore and microcatheters (28–32-gauge).

The spinal microcatheter was described first by Hurley and Lambert.[28] Their aim was to develop a sufficiently fine-bore catheter (32-gauge Rusch) which could be threaded through an appropriately fine spinal needle (26-gauge) into the CSF. Theoretically, com-

Table 2 Incidence of post-dural puncture headache (PDPH) (prospective studies)

Study	No. patients	Age (yr, mean)	Catheter (gauge)	PDPH (%)
Denny[15]	117	63	20	<1
Lui[38]	87	70	20	9.2
Mazze[41]	100	64	20/24	6
Van Gessel[75]	100	>65	20	0
Hurley[28]	58	50	32	4
De Andres[12]	65	33	32	3
Standl[68]	100	62.5	28	1

Table 3 Failure rate of continuous spinal anaesthesia (CSA). *one catheter broke

Study	No. patients	Catheter (gauge)	Failure (%)	Pro/ retrospective
Denny[15]	117	20	5.1	Prospective
Van Gessel[75]	100	20	0	Prospective
Sutter[69]	457	20	1.7	Retrospective
Mahisekar[40]	226	20	4	Retrospective
Horlocker[27]	474	20	3.2	Retrospective
Petros[51]	90	28*	4.4	Prospective
Standl[68]	100	28	0	Prospective
Chan[7]	55	27	16	Prospective
Horlocker[27]	127	28	3.9	Retrospective

Table 4 Complications of continuous spinal anaesthesia (CSA) (32-gauge) catheters

Study	No. patients	Cannot thread (%)	Failure (%)	Catheter Break (%)
Hurley[28]	58	10	15	3.4
Silvanto[62]	20	25	25	0
Pitkanen[52]	21	30	35	13
Klimscha[32]	26	—	1	0
De Andres[12]	65	3	8	0

Table 5 Cauda equina cases. 5LH=5% lidocaine hyperbaric, 1 Tetra=1% Tetracaine hyperbaric

Age (yr)	Ref. No.	Sex	Surg. position	Drug	Initial dose (mg)	Total dose (mg)	Catheter (gauge)
67	58	M	Lithotomy	5LH	150	290	28
60	58	M	?	5LH	150	220	28
68	56	M	Lithotomy	5LH	150	175	28
45	56	F	Supine	5LH	100	300	28
56	56	M	Supine	5LH	110	190	28
67	56	M	Supine	1 Tetra	20	37	20
76	27	F	Supine	5LH	30	120	20

pared with large-bore catheters, this would enable CSA to be performed in younger patients with a reduced risk of PDPH. Their initial study with the 32-gauge microcatheter in 58 patients in 1990 showed a 20% incidence of technical complications, which included failure to thread the catheter, inability to inject the local anaesthetic and inadequate anaesthesia, resulting in an incidence of failed spinal block of 15% and a 3.4% incidence of broken catheters (table 4).[28] Similar experiences were also reported by others (table 4).[12 52 62] The 32-gauge spinal microcatheter was difficult to handle, CSF could not be aspirated and it had a very high internal resistance, making injection of local anaesthetic very slow.

A 28-gauge catheter which could be passed through a 22-gauge spinal needle was then developed (Kendall). This catheter proved easier to use and did not have as many technical complications. Recent studies with 28-gauge catheters have shown a technical complication rate similar to that of large-bore catheters, including the incidence of PDPH.[27 51 68] The authors' own experience with this catheter revealed a higher incidence of slow onset and inadequate blocks compared with large-bore catheters.

However, it was not long before cases of neurological complications, in the form of cauda equina syndrome, were described after CSA with microcatheters.[56] Further reports of problems with the microcatheter technique[58] led the FDA in 1992 to ban the use of spinal catheters smaller than 24-gauge in the USA.[20] In all, approximately 12 cases of cauda equina syndrome after CSA with microcatheters have been reported.

Cauda equina syndrome and local anaesthetic toxicity

Cauda equina syndrome results from toxic damage to the nerve roots of the cauda equina, and is characterized by the following symptoms: low back pain, sensory disturbance in the saddle area, weakness of the legs, bowel and/or bladder dysfunction.[29]

In the first six cases of cauda equina syndrome reported, 28-gauge catheters and 5% hyperbaric lidocaine were used, except in one patient where a 20-gauge catheter and 1% hyperbaric tetracaine had been used.[56 58] All patients showed insufficient spread of anaesthesia which became adequate only after excessive doses of local anaesthetic had been injected. After operation it became evident that these patients had developed a serious neurological complication which was diagnosed as cauda equina syndrome. As an explanation, mechanical trauma to nerve roots was considered unlikely. Instead, it was postulated that this was a neurotoxic injury caused by pooling of highly concentrated local anaesthetic around the cauda equina.[56] The six first cases are summarized in table 5.

STUDIES WITH SPINAL MODELS

Studies using spinal column models have shown that insufficient spread of a hyperbaric local anaesthetic can occur if the catheter is positioned caudally and especially when the local anaesthetic is injected slowly.[17 35 55 57] Under such circumstances, the hyperbaric local anaesthetic could accumulate in the caudal end of the dural sac, without or with only little mixing with CSF, thus allowing exposure of the thinly protected nerve roots to an abnormally high concentration of the local anaesthetic. It was postulated that if this exposure time was long enough, the nerve roots could suffer from a toxic injury.

CLINICAL EVIDENCE

The suggested explanation is supported in clinical practice by the quoted remark of Tuohy (p. 1)[71] and by two reports of insufficient dermatomal spread of spinal anaesthesia caused by caudally positioned catheters which resulted in "failed CSA".[6 43] The first case was described by Morch, Rosenberg and Truant in 1957 in a remarkable study of intrathecal pharmacokinetics in patients during CSA with 5% hyperbaric lidocaine.[43] Large-bore catheters were inserted 17–20 cm into the CSF (aiming to place the tip at T11–12) both for injection of the local anaesthetic and to enable CSF samples to be withdrawn for analysis of lidocaine. In one patient, only restricted anaesthesia was detectable, despite injection of lidocaine 200 mg (in 2–3 separate doses). They found that the CSF concentration of lidocaine was approximately 5–7 times greater than in patients who had a successful block. Radiographically it was demonstrated that the catheter had gone caudally, and had curled up on itself with its end in the dural cul-de-sac at the level of the second sacral vertebra. Morch, Rosenberg and Truant stated that "as the lidocaine injected in this patient would probably form a pool in the dural sac it is easy to see why the concentration of lidocaine in the spinal fluid samples was so high".[43]

The second report is of two cases of failed CSA with 28-gauge spinal catheters.[6] In both patients a very restricted block (sacral) was demonstrated after an initial intrathecal injection of 1.5 ml (75 mg) of 5% hyperbaric lidocaine. Radiographic evidence showed that in both patients the catheters were placed caudally with contrast dye pooling sacrally.

In none of these cases were any neurological complications reported.

MIXING OF LOCAL ANAESTHETIC IN CSF: EFFECT OF SPEED OF INJECTION

Normally, injection of local anaesthetic via a spinal needle or a large-bore (spinal) catheter causes turbulence at its tip, enabling the local anaesthetic to mix and dilute with the CSF to become evenly distributed. This process varies with the rate of injection (ml s^{-1}), so that in principle, the faster the local anaesthetic is injected the more thoroughly it mixes with the CSF. However, because of its very high internal resistance it is difficult to inject local anaesthetic fast enough through a microcatheter to ensure adequate mixing with CSF.

With a caudally positioned catheter and the use of hyperbaric, highly concentrated local anaesthetics, such as 5% lidocaine, there is a risk that the poorly diluted local anaesthetic may remain in the caudal part of the dural sac for long enough to cause toxic lesions to the nerve roots.[36 56 58]

LOCAL ANAESTHETIC TOXICITY

Hyperbaric 5% lidocaine has been used uneventfully for more than 40 yr as a spinal anaesthetic, although mainly via a single injection technique, and it was not until recently that doubts were raised about the safety of this drug for spinal anaesthesia.[14 25 36 59 64] After reports of the described severe neurological complications and *in vitro* toxicity tests on frog nerves, some investigators have declared 5% hyperbaric lidocaine neurotoxic, and recommend anaesthetists not to use it for spinal anaesthesia.[14 16 36] However, the reported complications with 5% lidocaine were associated exclusively with its use in microcatheters. Lambert and Strichartz have shown *in vitro* with bullfrog sciatic nerves that both 5% lidocaine and 0.5% tetracaine were neurotoxic, whereas both 0.75% bupivacaine and 7.5% dextrose were not.[36]

What seems to have happened in patients who developed cauda equina syndrome is an incompatibility between a "normally" safe drug and a new injection device. Thus when combining the old reliable 5% hyperbaric lidocaine with microcatheters, a new risk of neurological complications was created. Theoretically, the use of very thin spinal needles, through which aspiration of CSF is difficult, could cause a similar situation to that described for microcatheters. Consequently, the FDA has recommended that 5% hyperbaric lidocaine should be diluted with an equal volume of CSF before injection.[21]

"Transient radicular irritation" (TRI) syndrome, sometimes seen after spinal anaesthesia, is frequently confused with the neurotoxic cauda equina syndrome.[14] TRI is a transient condition characterized by symmetric low back pain which usually resolves within 72 h. It normally responds to simple analgesics, and the described symptoms indicate that it is not a neurotoxic lesion.[14 25 59] TRI is neither concentration nor dose dependant in contrast with the cauda equina syndrome .[26 53]

Factors affecting intrathecal distribution of local anaesthetic

An even spread of local anaesthetic through the CSF giving an adequate block may not always occur with CSA[6 7 15 40 43 71] and newcomers to the use of CSA can be surprised by the occasional failure or restricted block. As mentioned previously, one reason for a caudally restricted block is a sacral position of the catheter.

CATHETER POSITION

Most anaesthetists intuitively aim to place the catheter in a cephalad direction to facilitate cranial spread of local anaesthetic. Its importance was described first by Tuohy[71] and this has been confirmed by two recent studies.[66 67] An important factor determining the direction of the catheter seems to be the length it is inserted into the subarachnoid space. Standl and Beck, in a study of 68 patients, found that microcatheters (28-gauge) inserted more than 4 cm had a 30% incidence of being placed caudally compared with 15% for those inserted less than 4 cm.[65] Other studies with 28-gauge catheters by the same group reported an incidence of caudal catheter placement of 16–35% (table 6).[65 67] The limited information available indicates a lower risk of caudal placement of 20-gauge catheters.[74]

In another study, Standl and colleagues found that the risk of caudal placement of 28-gauge catheters was reduced by using a directional spinal 22-gauge Sprotte needle.[67]

PATIENT POSITION

The position of the patient while the catheter is inserted is unlikely to influence the position of the catheter. Studies using 28-gauge microspinal catheters by Standl and colleagues have shown contrasting results. In one study they found that patients

Table 6 Incidence of caudally placed catheters

Study	Catheter (gauge)	No. patients	Incidence (%)
Van Gessel[74]	20	28	7
Standl[65]	28	68	16
Standl[67]	28	21	35

who had catheters inserted in the sitting position had only a 6% incidence of caudally directed catheters compared with 25% if placed with the patient in the right lateral position.[65] However, in the other study they found a 35% incidence of caudal catheters despite insertion in the sitting position.[67]

VOLUME AND DOSE OF LOCAL ANAESTHETIC

Provided isobaric solutions are used,[76] the spread of analgesia appears to be related mainly to the volume of local anaesthetic, while the total dose generally determines duration of block.[3 34 60 78] The height of the block is best controlled by titration of intermittent injections of small volumes of local anaesthetic through the catheter and assessment of block level after each injection.[2 8 15 32 34 60 67 69]

BARICITY

When equal volumes and doses of local anaesthetic are injected with patients supine, segmental spread of block is greater and onset is faster with hyperbaric than either isobaric or hypobaric solutions,[3 76] provided the spinal catheter is placed correctly. It should be remembered that plain bupivacaine solutions are slightly hypobaric at body temperature.[39]

CONCENTRATION

The concentration of local anaesthetic itself has little effect on the spread of spinal block, the spread primarily being a feature of speed of injection, volume and baricity.[3 34 61 77] Provided equal volumes are used, block duration is shorter with less concentrated local anaesthetics. Except for the smaller volume, no advantage seems to be gained by use of local anaesthetics of a higher concentration than used normally, for example in epidural anaesthesia.[5 77] As mentioned previously, highly concentrated local anaesthetics may cause neurotoxicity.

Indications and clinical use

SURGICAL

The main advantages of CSA over epidural anaesthesia and SSA are its easier technique and the possibility of providing an adequate level and duration of anaesthesia with small intermittent doses of local anaesthetic, which also minimizes the risks of cardiovascular and respiratory disturbances. These qualities are of special value for lower abdominal and lower limb surgery in elderly and high-risk patients; they constitute the primary indication for CSA.[2 8 15 19 23 32 35 40 60 69 73] When used in trauma patients, CSA appears to be associated with fewer technical problems and faster onset of anaesthesia compared with combined spinal–epidural anaesthesia.[79]

PAIN MANAGEMENT

Postoperative analgesia

There are a few published studies on the use of spinal catheters for postoperative analgesia,[1 4 48 49 68] and only one comparative study with epidural analgesia or other techniques has been published.[47] Postoperative analgesic regimens have been described for bupivacaine, morphine and diamorphine infusions. While experience with morphine and diamorphine has been successful,[4 47 49] that with bupivacaine solutions has been inconsistent, in terms of both motor block and hypotension.[48 68] There was also a high failure rate with microcatheters.[47 49 68] A recent study in patients after hip and knee arthroplasty showed that infusion of a combination of bupivacaine 1 mg h^{-1} and morphine 8 μg h^{-1} provided similar postoperative analgesia as bupivacaine alone infused at a rate of 2 mg h^{-1}, but with less motor block.[1] There was a high incidence of nausea and vomiting in the morphine group.

Chronic pain relief

For long-term analgesia in cancer patients, continuous spinal analgesia with dilute mixtures of bupivacaine and morphine, or bupivacaine and buprenorphine, were effective for several months, with few side effects and no signs of neurotoxic reactions.[31 63]

Adverse effects/side effects

CARDIOVASCULAR

Clinical studies have shown that haemodynamic stability is greater with CSA than with SSA or epidural anaesthesia. This is because of the possibility of titrating the level of anaesthesia with small incremental doses of local anaesthetic until adequate block is achieved.[2 3 15 19 32 34 60 67 69] From this aspect, isobaric solutions were more predictable to use than either hypo- or hyperbaric solutions.[3 76]

POST-DURAL PUNCTURE HEADACHE (PDPH)

The incidence of PDPH after CSA remains controversial, with widely differing reported incidences. Some prospective studies have shown a very low incidence, while others found incidences of 6–9% (table 2).[12 15 28 38 41 68 75] In retrospective studies, a generally low incidence of PDPH after CSA using large-bore catheters was found in older patients (table 1).[22 27 30 40 50] The few published studies of the incidence of PDPH after CSA with microcatheters in older patients have indicated no difference compared with what could be expected with large-bore spinal catheters.[12 28 62 68]

The incidence of PDPH after CSA is probably commensurate with the age of the patient, size of the needle used and dural puncture technique—the latter was demonstrated by Mihic, who detected a much lower incidence of PDPH if the dura was punctured with the needle bevel plane parallel to the axis of the spine as opposed to being at right angles.[42] In older patients, that is more than 60 yr, the incidence of PDPH is generally low after CSA with 20–24-gauge catheters (tables 1, 2). De Andres and colleagues found no difference in the incidence of PDPH after CSA with a 20-gauge catheter compared with SSA using 24-gauge Sprotte needles.[15]

In younger patients, experience with large-bore catheters is limited[22] and no large-scale prospective studies on the incidence of PDPH with microcatheters have been reported in this age group. However, a recent retrospective study showed a surprisingly high incidence of PDPH (33%) after use of 28-gauge microcatheters in obstetric patients for both vaginal and Caesarean delivery.[27]

Technical complications

ANAESTHETIC

The average failure rate of CSA with 20-gauge catheters is 2.5% (table 3).[7,15,27,40,51,68,69,75] This is comparable with the 4% found in a prospective study of 200 patients,[46] and with 3.1% in another prospective study of 1891 patients who all underwent SSA.[70] It is similar to failure rates of 0, 3.9 and 4.4% with 28-gauge catheters found in three studies[27,51,65] but in a fourth study, a 16% failure rate with 28-gauge catheters was reported (table 3).[7] In contrast, the overall failure rate for 32-gauge microspinal catheters was 17%[12,28,32,52,62] (table 4).

Occasionally the catheter can be difficult to thread. This incidence varies from 4.5 to 20%[15,51,67,75,76] and is usually a result of the needle tip being pushed too far into the subarachnoid space and lying too close to the opposite side of the spinal canal.[44] Often this can be overcome by withdrawing the needle slightly within the subarachnoid space and readvancing the catheter.

The incidence of transient paraesthesia on insertion of the catheter into the subarachnoid space can be as high as 24%.[75] While there is a potential risk of infection when the dura is punctured, especially with long-term use, there are no reports of infective meningitis or sepsis after CSA.

POSTOPERATIVE PAIN MANAGEMENT

There are limited data on the technical complications of the use of spinal catheters for postoperative pain control. The problems encountered range from disconnection of the catheter from the filter, obstruction of the catheter as a result of kinking and migration of the catheter tip out of the CSF.[4,48,49,68] The 19% failure rate with 28-gauge catheters in one study made the authors change to 22-gauge catheters which reduced the failure rate to only 4%.[49]

Needle design

It is well known that the risk of PDPH after SSA is lower if pencil-point spinal needles are used rather than cutting edged ones of similar gauge.[24] In spite of this, surprisingly little attention has been paid to the use of pencil-point needles with CSA. The other potential advantage with the use of this type of needle is that the side hole would enable a more accurate placement of the catheter, as was found in a recent study by Standl and colleagues.[67] Further studies need to be performed to evaluate the use of pencil-point needles for CSA with reference to the incidence of PDPH, particularly in younger patients.

Recently, a new 22-gauge spinal catheter over a 27-gauge needle has been developed with a thin wire attached to the needle, with the tip of the wire protruding from the injection end of the catheter ("Spinocath" B Braun).[45] A modified Tuohy needle is placed in the epidural space, the "Spinocath" is then pushed through the dura into the CSF and the needle is pulled out leaving the catheter in the CSF. The theoretical advantage of this system is that the hole in the dura is the same size as the catheter, thus minimizing CSF leak. However, there is little published information on this technique and prospective studies are needed to evaluate its use, particularly in younger patients.

Conclusion

Continuous spinal anaesthesia is a well established technique and has clear advantages over epidural and single shot spinal anaesthesia, especially in elderly or high-risk patients. CSA offers possibilities of reduced interference with the cardiovascular and respiratory systems by allowing the anaesthetist to titrate small doses of local anaesthetic to reach the required level of spinal anaesthesia, and the duration can be extended to match the needs of prolonged surgery. As with all techniques, proper training is vital for the optimal use of CSA.

The use of 20-gauge catheters for CSA can be recommended in older patients (i.e. more than 60 yr) in whom the incidence of PDPH is low. Most experience of large-bore catheters has been gained with 20-gauge catheters and 18-gauge needles, and there is little published data on the use of 22- or 24-gauge catheters. Therefore, it is not possible to say if there is any benefit from the use of these thinner catheters. Experience to date indicates that there is no advantage in the use of microcatheters.

There are little data on the use of CSA in younger patients, with particular reference to the incidence of PDPH; at present it cannot be recommended for routine use in younger patients. In obstetric patients, CSA, in common with single shot spinal anaesthesia, seems to carry an increased risk of PDPH, which reduces its advantages in these patients.

Bupivacaine (0.25–0.5%) appears to be a safe local anaesthetic for use with CSA. The use of short-acting, high concentration, hyperbaric local anaesthetics for CSA is not recommended .

In summary, correctly used, CSA is an effective, reliable and safe technique.

References

1. Bachman M, Laakso E, Niemi L, Rosenberg PH, Pitkanen M. Intrathecal infusion of bupivacaine with or without morphine for postoperative analgesia after hip and knee arthroplasty. *British Journal of Anaesthesia* 1997; 78: 666–670
2. Brown S. Fractional segmental spinal anesthesia in poor risk surgical patients. *Anesthesiology* 1952; 13: 416–428
3 Brown DT, Wildsmith JAW, Covino BG, Scott DB Effect of baricity on spinal anaesthesia with amethocaine. *British Journal of Anaesthesia* 1980; 52: 589–596.
4. Burchett KR, Denny NM. Initial experience of continuous subarachnoid diamorphine infusion for postoperative pain relief. *Regional Anesthesia* 1991; 16: 253–256
5. Chambers WA, Littlewood DG, Edstrom HH, Scott DB Spinal anaesthesia with hyperbaric bupivacaine: effects of concentration and volume administration *British Journal of Anaesthesia* 1982; 54: 75–80.
6 Chan VWS, Smyth RJ. Radiographic examination of catheter position in restricted sacral block after continuous spinal anesthesia. *Anesthesia and Analgesia* 1992; 75: 449–452

7. Chan VWS, Chung F, Gomez M, Seyone C, Baylon G. Anesthetic and hemodynamic effects of single versus incremental titration of hyperbaric spinal lidocaine through microcatheter. *Anesthesia and Analgesia* 1994; 79: 117–123.
8. Collard CD, Eappen S, Lynch EP, Concepcion M. Continuous spinal anesthesia with invasive hemodynamic monitoring for surgical repair of the hip in two patients with severe aortic stenosis. *Anesthesia and Analgesia* 1995; **81**: 195–198.
9. Cohen S, Amar D, Pantuck EJ, Singer N, Divon M. Decreased incidence of headache after accidental dural puncture in caesarean delivery patients receiving continuous intrathecal analgesia. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 716–718.
10. Curbello MM. Continuous peridural segmental anesthesia by means of a urethral catheter. *Current Research in Anesthesiology* 1949; **28**: 13–16.
11. Dean HP. Discussion on the relative value of inhalation and injection methods of inducing anaesthesia. *British Medical Journal* 1907; **2**: 869–877.
12. De Andres J, Bellver J, Bolinches R. Comparison of continuous spinal anaesthesia using a 32G catheter with anaesthesia using a single dose 24G atraumatic needle in young patients. *British Journal of Anaesthesia* 1994; **73**: 747–750.
13. De Andres JA, Febre E, Bellver J, Bolinches R. Continuous spinal anaesthesia versus single dosing. A comparative study. *European Journal of Anaesthesiology* 1995; **12**: 135–140.
14. de Jong RH. Last round for a "heavyweight"? *Anesthesia and Analgesia* 1994; **78**: 3–4.
15. Denny N, Masters R, Pearson D, Read J, Sihota M, Selander DE. Postdural puncture headache after continuous spinal anesthesia. *Anesthesia and Analgesia* 1987; **66**: 791–794.
16. Denny NM. Continuous spinal anaesthesia and cauda equina syndrome. *Anaesthesia* 1995; **50**: 474.
17. Drasner K. Models for local anesthetic toxicity from continuous spinal anesthesia. *Regional Anesthesia* 1993; **18**: 434–438.
18. Dripps RD. A comparison of the malleable needle and catheter techniques for continuous spinal anesthesia. *New York Journal of Medicine* 1950; **50**: 1595–1599.
19. Favarel-Garrigues JF, Sztark F, Petietjean ME, Thicoipe M, Lassie P, Dabad P. Hemodynamic effects of spinal anesthesia in the elderly: single dose versus titration through a catheter. *Anesthesia and Analgesia* 1996; **82**: 312–316.
20. FDA. Safety alert. Cauda equina syndrome associated with use of small-bore catheters in continuous spinal anesthesia. May 29, 1992.
21. F-D-C Reports—"Pink Sheet". Astra 5% hyperbaric xylocaine labeling for spinal anesthesia should recommend 1-to-1 drug dilution to reduce neurotoxicity risk. FDA CMTE, concludes June 13, 1994.
22. Giuffrida JG, Bizzarri DV, Masi R, Bondoc R. Continuous procaine spinal anesthesia for cesarian section. *Anesthesia and Analgesia* 1972; **51**: 117–124.
23. Grace D, Orr DA. Continuous spinal anaesthesia in acute respiratory failure *Anaesthesia* 1993; **48**: 226–228.
24. Halpern S, Preston R. Postdural puncture headache and spinal needle design. *Anesthesiology* 1994; **81**: 1376–1388.
25. Hampl KF, Schneider MC, Ummenhofer W, Drewe J. Transient neurologic symptoms after spinal anesthesia. *Anesthesia and Analgesia* 1995; **81**: 1148–1533.
26. Hampl KF, Schneider MC, Pargger H, Gut J, Drewe J, Drasner K. A similar incidence of transient neurological symptoms after spinal anesthesia with 2% and 5% lidocaine. *Anesthesia and Analgesia* 1996; **83**: 1051–1054.
27. Horlocker TT, McGregor DG, Matsushige DK, Chantigian RC, Schroeder DR, Besse JA. Neurological complications of 603 continuous spinal anesthetics using macrocatheter and microcatheter techniques. *Anesthesia and Analgesia* 1997; **84**: 1063–1070.
28. Hurley RJ, Lambert DH. Continuous spinal anesthesia with a microcatheter technique. Preliminary experience. *Anesthesia and Analgesia* 1990; **70**: 97–102.
29. Jaradeh S. Cauda equina syndrome: A neurologist's perspective. *Regional Anesthesia* 1993; **18**: 473–480.
30. Kallos T, Smith TC. Continuous spinal anesthesia with hypobaric tetracaine for hip surgery in lateral decubitus. *Anesthesia and Analgesia* 1972; **51**: 76–62.
31. Karlsson P-Å, Nordborg C, Sjöberg M, Nitescu P, Appelgren L, Curelaru I. Neuropathological findings after long-term intrathecal infusion of buprenorphine and bupivacaine for pain treatment in cancer patients. *European Journal of Pain* 1994; **15,4**: 69–76.
32. Klimscha W, Weinstabl C, Ilias W, Mayer N, Kashanipour A, Scheider B, Hammerle A. Continuous spinal anesthesia with a microcatheter and low-dose bupivacaine decreases the hemodynamic effects of centro-neuroaxis blocks in elderly patients. *Anesthesia and Analgesia* 1993; **77**: 275–280.
33. Kopacz D Continuous spinal anaesthesia for abdominal surgery in a patient receiving amiodorone. *Canadian Journal of Anaesthesia* 1991; **38**: 341–344.
34. Labaille L, Benhamou D, Westermann J. Hemodynamic effects of continuous spinal anesthesia: A comparative study between low and high doses of bupivacaine. *Regional Anesthesia* 1992, **17**: 193–196.
35. Lambert DH, Hurley RJ. Cauda equina syndrome and continuous spinal anesthesia. *Anesthesia and Analgesia* 1991; **72**: 817–819.
36. Lambert DH, Strichartz GR. Irreversible conduction block in isolated nerve by high concentrations of local anesthetics. *Anesthesiology* 1994, **80**. 1082–1093.
37. Lemmon WT. A method for continuous spinal anesthesia. *Annals of Surgery* 1940; **111**: 144.
38. Liu N, Montefiore A, Kermarec N, Rauss A, Bonnet F. Prolonged placement of spinal catheters does not prevent postdural puncture headache. *Regional Anesthesia* 1993; **18**: 110–113.
39. Logan MR, McClure JH, Wildsmith JA. Plain bupivacaine: an unpredictable spinal anaesthetic agent. *British Journal of Anaesthesia* 1986; **58**: 292–296.
40. Mahisekar UL, Winnie AP, Vasireddy AO, Masters RW. Continuous spinal anesthesia and postdural puncture headache. A retrospective study. *Regional Anesthesia* 1991; **16**: 107–111.
41. Mazze RI, Fujinaga M. Postdural puncture headache after continuous spinal anesthesia with 18G and 20G needles. *Regional Anesthesia* 1993; **18**: 447–451.
42. Mihic DN. Postspinal headache and relationship of needle bevel to longitudinal dural fibres. *Regional Anesthesia* 1985; **10**: 76–81.
43. Morch ET, Rosenberg MK, Truant AT. Lidocaine for spinal anesthesia. A study of the concentration in the spinal fluid. *Acta Anaesthesiologica Scandinavica* 1957; **1**: 105–115.
44. Mollmann M, Holst D, Lubbesmeyer H, Lawin P. Continuous spinal anesthesia: Mechanical and technical problems of catheter placement. *Regional Anesthesia* 1993; **18**: 469–472
45. Mollmann M, Van Steenberge A, Sell A, Pitkanen M, Holst D, Van Dongen A, Berg S. Spinocath, a new approach to continuous spinal anaesthesia—Preliminary results of a multicentre trial. *International Monitor on Regional Anaesthesia* 1996; **8**: 74.
46. Munhall RJ, Sukhani R, Winnie AP. Incidence and etiology of failed spinal anesthetics in a university hospital: A prospective study. *Anesthesia and Analgesia* 1988; **67**: 843–848.
47. Niemi L, Pitkanen M, Tuominen M, Rosenberg PH. Technical problems and side effects associated with continuous intrathecal or extradural post-operative analgesia in patients undergoing hip arthroplasty. *European Journal of Anaesthesiology* 1994; **11**: 469–474.
48. Niemi L, Pitkanen M, Dunkel P Laakso E, Rosenberg PH. Evaluation of the usefulness of intrathecal bupivacaine infusion for analgesia after hip and knee arthroplasty. *British Journal of Anaesthesia* 1996; **77**: 544–545.
49. Niemi L, Pitkanen MT, Tuominen MK, Rosenberg PH. Comparison of intrathecal fentanyl infusion with intrathecal morphine infusion or bolus for postoperative pain relief after hip arthroplasty. *Anesthesia and Analgesia* 1993; **77**: 126–130.
50. Peterson DO, Borup LJ, Chestnut JS. Continuous spinal anesthesia, case review and discussion. *Regional Anesthesia* 1983; **8**: 109–113.
51. Petros AJ, Barnard M, Smith D, Ronzoni G. Continuous spinal anesthesia: Dose requirements and characteristics of the block. *Regional Anesthesia* 1993; **18**: 52–54.
52. Pitkanen M, Tuominem M, Rosenberg P, Wahlstrom T. Technical and light microscopic comparison of four small catheters used for continuous spinal anesthesia. *Regional Anesthesia* 1992; **17**: 288–291.
53. Pollock JE, Neal JM, Stephenson CA, Wiley CE. Prospective study of transient radicular irritation in patients undergoing spinal anesthesia. *Anesthesiology* 1996; **84**: 1361–1367.
54. Rao TLK, El-Etr AE. Anticoagulation following placement of extradural and subarachnoid catheters: an evaluation of neurologic sequelae. *Anesthesiology* 1981; **55**: 618–620.
55. Rigler ML, Drasner K. Distribution of catheter-injected local anesthetic in a model of the subarachnoid space. *Anesthesiology* 1991; **75**: 684–692.

56. Rigler ML, Drasner K, Krejcie TC, Yelish SJ, Scholnick FT, Defontes J, Bohner D. Cauda equina syndrome after continuous spinal anesthesia. *Anesthesia and Analgesia* 1991; **72**: 275–281.
57. Ross BK, Coda B, Heath CH. Local anesthetic distribution in a spinal model: A possible mechanism of neurologic injury after continuous spinal anesthesia. *Regional Anesthesia* 1992; 17: 69–77.
58. Schell RM, Brauer FS, Cole DJ, Applegate RL. Persistent sacral nerve root defects after continuous spinal anaesthesia. *Canadian Journal of Anaesthesia* 1991; **38**: 908–911.
59. Schneider M, Ettlin T, Kaufman M, Schumacher P, Urwyler A, Hampl K, Hochsetter A. Transient neurologic toxicity after hyperbaric subarachnoid anesthesia with 5% lidocaine. *Anesthesia and Analgesia* 1993; **76**: 1154–1157.
60. Schnider W, Mueller-Duysing S, Johr M, Gerber H. Incremental dosing versus single-dose spinal anesthesia and hemodynamic stability. *Anesthesia and Analgesia* 1993; **77**: 1174–1178.
61. Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edstrom H, Covino BG. A dose response study of bupivacaine for spinal anesthesia. *Anesthesia and Analgesia* 1983; **62**: 931–935.
62. Silvanto M, Pitkanen M, Tuominen M, Rosenberg PH. Technical problems associated with the use of 32G and 22G spinal catheters. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 295–299.
63. Sjöberg M, Karlsson P-A, Nordborg C, Wallgren A, Nitescu P, Appelgren L, Linder L-E, Curelaru I. Neuropathologic findings after long-term intrathecal infusion of morphine and bupivacaine for pain treatment in cancer patients. *Anesthesiology* 1992; **76**: 173–186.
64. Sjostrom S, Blass J. Severe pain in both legs after spinal anaesthesia with hyperbaric 5% lignocaine solution. *Anaesthesia* 1994; **49**: 700–702.
65. Standl T, Beck H. Radiological examination of the intrathecal position of microcatheters in continuous spinal anaesthesia. *British Journal of Anaesthesia* 1993; 71: 803–806.
66. Standl T, Beck H. Influence of the subarachnoid position of micro-catheters on the onset of analgesia and dose of plain bupivacaine 0.5% in continuous spinal anesthesia. *Regional Anesthesia* 1994; **19**: 231–236.
67. Standl T, Eckert S, Rundshagen I, Schulte am Esch J. A directional needle improves effectiveness and reduces complications of microcatheter continuous spinal anaesthesia. *Canadian Journal of Anaesthesia* 1995; **42**: 701–705.
68. Standl T, Eckert S, Schulte am Esch J. Microcatheter continuous spinal anaesthesia in the post-operative period: a prospective study of its effectiveness and complications. *European Journal of Anaesthesiology* 1995; **12**: 273–279.
69. Sutter P-A, Gamulin Z, Forster A. Comparison of continuous spinal and continuous extradural anaesthesia for lower limb surgery in elderly patients. A retrospective study. *Anaesthesia* 1989; **44**: 47–50.
70. Tarkkila PJ. Incidence and causes of failed spinal anesthetics in a university hospital: A prospective study. *Regional Anesthesia* 1991; **16**: 48–52.
71. Tuohy EB. Continuous spinal anesthesia, its usefulness and technique involved. *Anesthesiology* 1944; **5**: 142–148.
72. Tuohy EB. Continuous spinal anesthesia· A new method of utilizing ureteral catheter. *Surgery Clinics of North America* 1945; **25**: 834–840.
73. Underwood RJ. Continuous spinal anesthesia in physical status group IV patients. *Anesthesia and Analgesia* 1968; 47: 18–26.
74. Van Gessel EF, Forster A, Gamulin Z. Continuous spinal anesthesia: Where do spinal catheters go? *Anesthesia and Analgesia* 1993; **76**: 1004–1007.
75. Van Gessel E, Forster A, Gamulin Z. A prospective study of feasibility of continuous spinal anesthesia in a University hospital. *Anesthesia and Analgesia* 1995; **80**: 880–885.
76. Van Gessel EF, Forster A, Schweizer A, Gamulin Z Comparison of hypobaric, hyperbaric and isobaric solutions of bupivacaine during continuous spinal anesthesia. *Anesthesia and Analgesia* 1991; 72: 779–784.
77. Van Zundert AAJ, Grouls RJE, Korsten HHM, Lambert DH. Spinal anesthesia volume or concentration—What matters? *Regional Anesthesia* 1996; **21**: 112–118.
78. Wildsmith JAW, McClure JH, Brown DT, Scott DB. Effects of posture on the spread of isobaric and hyperbaric amethocaine. *British Journal of Anaesthesia* 1981; 53. 273–278.
79. Wilhelm S, Standl T, Burmeister M, Kessler G, Schulte am Esch J. Comparison of continuous spinal with combined spinal-extradural anesthesia using plain 0. 5% bupivacaine in trauma patients. *Anesthesia and Analgesia* 1997; **85**: 69–74.

British Journal of Anaesthesia 1998; **81**: 598–600

SHORT COMMUNICATIONS

The CYP 3A4 inhibitor itraconazole has no effect on the pharmacokinetics of i.v. fentanyl[†]

V. J. PALKAMA, P. J. NEUVONEN AND K. T. OLKKOLA

Summary

We studied 10 healthy volunteers given itraconazole 200 mg orally, once daily or placebo for 4 days in a crossover study. I.v. fentanyl 3 μg kg^{-1} was given on day 4. Plasma concentrations of fentanyl were measured by radioimmunoassay and ventilatory frequency and peripheral arteriolar oxygen saturation were also measured. Fentanyl-induced subjective effects (drowsiness, itching, nausea, performance, feeling of drug effect) were measured by visual analogue scales. The pharmacokinetics and pharmacodynamics of fentanyl were similar after both itraconazole and placebo. Thus although itraconazole is a strong inhibitor of the cytochrome 3A enzymes responsible for metabolism of fentanyl *in vitro*, it did not affect the i.v. pharmacokinetics of fentanyl in humans. (*Br. J. Anaesth.* 1998; **81**: 598–600).

Keywords: analgesics opioid, fentanyl; pharmacology, itraconazole; pharmacokinetics, fentanyl; enzymes, cytochrome 3A

Fentanyl is a synthetic opioid and its metabolism is mediated by CYP 3A4.[1] As there is no information on the effect of CYP 3A4 inhibitors on the metabolism of fentanyl in humans, we have studied the possible interaction of the CYP 3A4 inhibitor, itraconazole, with i.v. fentanyl.

Methods and results

Based on previous studies,[2] we calculated that eight subjects would be required to demonstrate a 20% difference in values for fentanyl clearance (which was regarded as the primary pharmacokinetic end-point) at a level of significance of P=0.05 and a power of 80%. Thus after obtaining approval from our institute and written informed consent, we studied 10 healthy volunteers (five women), aged 19–24 yr, weighing 53–75 kg. None was receiving regular medications except for two females who were using contraceptive steroids.

A randomized, double-blind, cross-over study design was used at intervals of 4 weeks. Subjects were given either itraconazole 200 mg (Sporanox, Janssen, Belgium) orally, once daily at 0700 or placebo for 4 days. On day 4, fentanyl (Fentanyl 50 μg ml^{-1}, Janssen, Belgium) 3 μg kg^{-1} was given i.v., 1 h after oral administration of itraconazole/placebo over 2 min.

Venous blood samples were obtained immediately before injection of fentanyl and 0.25, 0.5, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 24 h after administration. Fentanyl concentrations were analysed by a specific radioimmunoassay method.[3] The sensitivity of the method for fentanyl was 0.1 ng ml^{-1} and the coefficient of variation (cv) was 11.8% at mean 0.179 ng ml^{-1}, 8.1% at mean 0.596 ng ml^{-1} and 7.6% at mean 2.98 ng ml^{-1} (n=6 at each concentration). Concentrations of itraconazole were analysed by HPLC.[4]

Standard non-compartmental methods were used to calculate plasma clearance (Cl) and apparent steady state volume of distribution (V^{ss}) of fentanyl. Elimination half-lives ($T_{1/2}$) were calculated using log-linear regression. Peripheral arteriolar oxygen saturation (Sp_{O_2}) was measured continuously during the first 2 h after administration of fentanyl, and thereafter Sp_{O_2} was recorded at blood sampling together with ventilatory frequency and heart rate until 10 h after administration of fentanyl. Subjective effects were recorded on five horizontal visual analogue scales for 10 h at blood sampling (no effects of the drug—very strong effects of the drug; alert—drowsy; very good performance—very poor performance; no nausea—lots of nausea; no itching—lots of itching).

Pharmacokinetic and pharmacodynamic variables between phases were compared using the Wilcoxon matched pairs test. Differences were regarded as statistically significant if P<0.05.

There were no statistically significant differences in any of the pharmacokinetic or pharmacodynamic variables between phases (fig. 1). Values of Cl, V^{ss} and $T_{1/2}$ for fentanyl during the placebo phase were mean 23.9 (SD 9.9) ml kg^{-1} min^{-1}, 5.2 (1.9) litre kg^{-1} and 4.4 (2.3–6.9) h (median (range)). The corresponding values during the itraconazole phase were 22.0 (12.7) ml kg^{-1} min^{-1}, 5.4 (1.9) litre kg^{-1} and 4.8 (2.4–18.2) h, respectively. The elimination half-life was not calculated when fentanyl concentration decreased to less than the detection limit but then exceeded this limit later (one subject in the placebo phase and one subject in the itraconazole phase). The concentration of itraconazole at the time of administration of fentanyl during the itraconazole phase was

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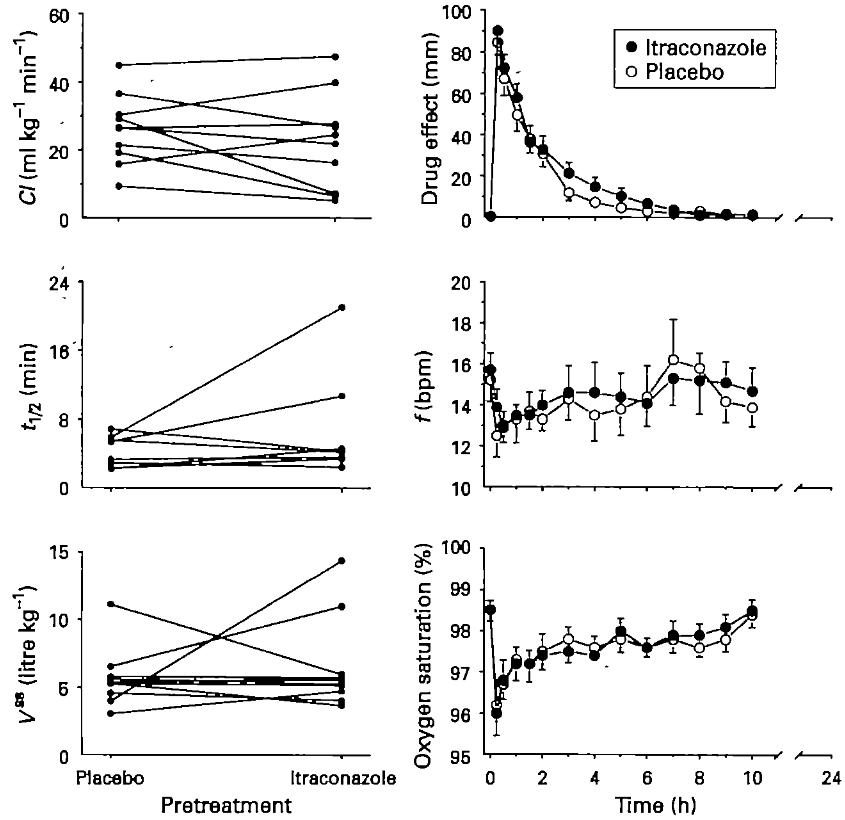

Figure 1 Individual values for clearance (Cl), elimination half-life ($T_{1/2}$) and steady state volume of distribution (V^{ss}) of fentanyl in 10 subjects during placebo and itraconazole treatments (left), and the subjective drug effects of fentanyl 3 μg kg^{-1} (visual analogue scale: no effect of the drug—very strong effect of the drug), ventilatory frequency (f) and peripheral arteriolar oxygen saturation (right) after pretreatment with oral itraconazole 200 mg or placebo for 4 days in 10 healthy volunteers.

155 (49–412) ng ml^{-1} (median (range)). We have shown previously that itraconazole at a concentration of 80 ng ml^{-1} effectively inhibits CYP 3A4.[5]

Comment

In our study, itraconazole had no statistically significant effects on the pharmacokinetics or pharmacodynamics of fentanyl. The mean value for V^{ss} was virtually unchanged by concomitant administration of itraconazole, and the small 9% decrease in mean fentanyl Cl was not statistically significant. All pharmacological effect *vs* time curves were essentially the same between the two phases.

Fentanyl is metabolized by the CYP3A4 isoenzyme in human liver.[1] Itraconazole is a strong inhibitor of CYP3A4 *in vitro* and it has been shown to markedly reduce the clearance of substrates of CYP3A4, such as midazolam[5] in humans. We were unable to identify any effects of itraconazole on fentanyl elimination. Compared with alfentanil, the elimination of which is strongly inhibited by, for instance, concomitant therapy with the macrolide antibiotic troleandomycin,[6] there appears to be some discrepancy between fentanyl studies *in vitro* and in humans. In contrast, similar results have also been obtained with sufentanil, which is metabolized *in vitro* by CYP3A4 but whose pharmacokinetics in humans are also virtually unaffected by prior administration of the enzyme inhibitor, erythromycin.[1]

The different effects of the inhibitors of CYP3A4 on the pharmacokinetics of fentanyl, alfentanil and sufentanil in humans can be explained by the differences in the pharmacokinetics of these opioids. Fentanyl, alfentanil and sufentanil are eliminated mainly by metabolism,[2] but hepatic extraction ratios vary greatly. Alfentanil has an extraction ratio of 0.3–0.5 and the corresponding values for fentanyl and sufentanil are 0.8–1.0 and 0.7–0.9, respectively.[2] Because fentanyl has a very high extraction ratio, it can be estimated that even rather large changes in the activity of the enzymes metabolizing fentanyl are unlikely to significantly affect its pharmacokinetics. However, clearance of alfentanil is readily altered when the activity of CYP3A4 enzymes change.[6]

In our study, small doses of fentanyl were used. Because healthy volunteers were studied, higher doses would have necessitated the use of opioid antagonists or alternatively the study could have been performed during clinical anaesthesia. However, both of these alternatives might have disturbed the assessment of the possible interaction between itraconazole and fentanyl, as all drugs administered concomitantly may interact with each other. Therefore, we chose to study healthy volunteers using a fentanyl dose which is commonly used during induction of general anaesthesia. Although our study did not allow definitive conclusions on the possible effect of oral itraconazole on higher doses of fentanyl, it can be anticipated that itraconazole causes no major changes in the pharmacokinetics of the usual doses of fentanyl administered during surgery. In these instances, fentanyl can be used in normal doses with itraconazole and probably also with other CYP3A4 inhibitors. Further studies are needed to evaluate the effect of itraconazole on high-dose fentanyl anaesthesia.

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References

1. Tateishi T, Krivoruk Y, Ueng Y-F, Wood AJJ, Guengerich FP, Wood M. Identification of human liver cytochrome P-450 3A4 as the enzyme responsible for fentanyl and sufentanil N-dealkylation. *Anesthesia and Analgesia* 1996; **82**: 167–172.
2. Bailey PL, Stanley TH. Intravenous opioid anesthetics. In: Miller RD, ed. *Anesthesia*. New York: 1994; 353–357.
3. Woestenborghs R, Stanski D, Scott J, Heykants J. Assay of methods for fentanyl in serum: gas–liquid chromatography versus radioimmunoassay. *Anesthesiology* 1987; **67**: 85–90.
4. Woestenborgshs R, Lorreyne W, Heykants J. Determination of itraconazole in plasma and animal tissues by high-performance liquid chromatography. *Journal of Chromatography* 1987; **413**: 332–337.
5. Olkkola KT, Ahonen J, Neuvonen PJ. The effect of the systemic antimycotics itraconazole and fluconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Anesthesia and Analgesia* 1996; **82**: 511–516.
6. Kharasch ED, Russel M, Mautz D, Thummel KE, Kunze KL, Bowdle A, Cox K. The role of cytochrome P450 3A4 in alfentanil clearance. *Anesthesiology* 1997; **87**: 36–50.

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Thiopental attenuates relaxation and cyclic GMP production in vascular smooth muscle of endotoxin-treated rat aorta, independent of nitric oxide production

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Summary

As thiopental (thiopentone) suppresses cyclic GMP (cGMP) formation produced by nitric oxide donor drugs, we have tested if it suppresses cGMP formation and increases vascular tone after induction of calcium–calmodulin-independent nitric oxide synthase (iNOS). Rat aortic rings were treated with *Escherichia coli* lipopolysaccharide (LPS) 1 μg ml^{-1} for 4 h, and the effects of thiopental on tension, cGMP concentrations and nitrite accumulation were determined. Thiopental 0.3 mmol litre^{-1} reduced the tension of phenylephrine-precontracted aortic rings before LPS treatment, but caused no significant effects on tension in the presence of L-arginine 10 μmol litre^{-1} after LPS treatment. L-Arginine 1 μmol litre^{-1} to 1 mmol litre^{-1} increased concentrations of cGMP in LPS-treated aorta in a concentration-dependent manner. This was reduced by thiopental 0.3–1 mmol litre^{-1}. Treatment with L-arginine 1 mmol litre^{-1} increased concentrations of nitrite, the end product of nitric oxide; this was not affected by thiopental 1 mmol litre^{-1}. We conclude that thiopental suppressed cGMP formation in iNOS-induced vascular smooth muscle without affecting nitric oxide production. (*Br. J. Anaesth.* 1998; **81**: 601–602).

Keywords: pharmacology, nitric oxide; anaesthetics i v., thiopental; muscle vascular,responses; rat

Expression of calcium–calmodulin-independent nitric oxide synthase (iNOS) is one aspect of the pathogenesis of profound hypotension in septic patients.[1,2] Constitutive nitric oxide synthase (cNOS), which includes endothelial (eNOS) and neuronal (nNOS) nitric oxide synthase, is activated only when cytosolic calcium is increased. However, iNOS converts L-arginine to nitric oxide, independent of calcium. Nitric oxide activates guanylate cyclase (GC) and increases production of cyclic GMP (cGMP), which then leads to vasorelaxation.

Until now, no anaesthetic has been shown to suppress the effect of iNOS.[1] Kesler and colleagues[2] showed that thiopental augmented iNOS induction in vascular smooth muscle, but the effect on cGMP production, when iNOS was induced, was not examined. As thiopental (thiopentone) strongly suppresses cGMP formation induced by a nitric oxide donor drug, in addition to that induced by activation of eNOS and nNOS,[3,4] we anticipated that this anaesthetic may also suppress cGMP formation induced by iNOS. Therefore, we have tested this hypothesis by evaluating the effect of thiopental on tension and production of nitric oxide and cGMP in endotoxin-treated vascular smooth muscle.

Methods and results

In accordance with the standards of the Kyoto University Animal Use Committee, descending thoracic aortae were harvested from Wistar rats (weighing 250–350 g). Four to six endothelium-denuded ring segments were prepared from each aorta and placed in Krebs bicarbonate solution of the following composition (mmol litre^{-1}): NaCl 118.2, KCl 4.6, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 24.8, glucose 10 (pH 7.35–7.45), which was aerated with a mixture of 95% oxygen and 5% carbon dioxide and maintained at 36.5–37.5°C. The aortic rings, except for those for the time-controlled studies, were bathed in Krebs solution containing *Escherichia coli* lipopolysaccharide (LPS) 1 μg ml^{-1} for 4 h, and then washed and equilibrated for 1 h.

Vascular rings for measurement of isometric tension were mounted under a resting tension of 3.0 g. After attainment of equilibrium, the rings were exposed to KCl 30 mmol litre^{-1} to induce contraction, which was taken as the 100% level for each ring throughout the experiment. The absolute value for KCl-induced contractions was 585 (SEM 217) mg (n=26). Rings were then exposed to acetylcholine 10 μmol litre^{-1} to confirm endothelial denudation. None showed relaxation in response to acetylcholine.

After washing, the rings were exposed to phenylephrine 0.3 μmol litre^{-1} to induce sustained contraction (189 (9.2) %, n=26). Subsequent exposure to thiopental 0.3 and 1 mmol litre^{-1} reduced the tension to 154 (8.2) % (P=0.0030) and 33.2 (5.8) % ($P \leq 0.0001$), respectively (n=13 each). After LPS treatment, addition of phenylephrine 0.3 μmol ml^{-1} to

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the bath produced sustained contraction (162 (10.7) %, *n*=26). The subsequent 10 min of exposure to L-arginine 10 μmol ml^{-1} decreased this tension to 59.7 (9.6) % ($P \leq 0.0001$) (*n*=12), while L-nitro-N-arginine (L-NNA) 30 μmol ml^{-1} increased it to 231 (14.8) % ($P \leq 0.0001$) (*n*=14). Exposure to thiopental 0.3 and 1 mmol litre^{-1} did not affect the tension of L-arginine-exposed rings but the response of L-NNA-exposed rings to thiopental was similar to that of LPS-untreated rings.

The rings for cGMP and nitric oxide measurements were suspended in organ baths without tension, treated with LPS and, after washing, with thiopental 0.3 or 1 mmol litre^{-1} or without (control) for 20 min. Those for cGMP measurement were exposed to L-arginine 1 μmol litre^{-1} to 1 mmol litre^{-1} for 12 min. cGMP content in each sample was assessed by radioimmunoassay.[3 4] cGMP production in LPS-treated aortae was dependent on the concentration of L-arginine, and was suppressed by thiopental 0.3–1 mmol litre^{-1} (fig. 1).

Rings for assessment of nitric oxide formation were transferred to plastic microtubes containing 1 ml of Krebs solution with L-arginine 1 mmol ml^{-1}, with or without thiopental 1 mmol litre^{-1}, and incubated for 10 min. A sample of bath fluid was mixed with 8 vol% of *Aspergillus* nitrate reductase 5 iu ml^{-1} and 40 vol% ß-NADPH 500 mmol litre^{-1}, and equilibrated at room temperature for 1 h to allow conversion of nitrate to nitrite.[5] Nitrite concentration was measured using a nitric oxide analyser (NOA Model 270B, Sievers Research Inc., Boulder, CO, USA). The increases in nitrite in iNOS-induced aortae during 10 min of incubation in the absence and presence of thiopental 1 mmol litre^{-1} were 49.2 (19.3) and 52.2 (14.0) μmol/g wet weight, respectively (P=0.9024) (*n*=6 each).

The effects of thiopental on tension were analysed using the Student's *t* test for paired data and the effects on nitrite production were analysed using the Student's *t* test for unpaired data. Other analyses were by factorial analysis of variance (ANOVA) with Scheff's *F* test, or repeated measure ANOVA. Data are expressed as mean (SEM), *n*=number of animals tested and differences at $P<0.05$ were considered significant.

Comment

Our finding that thiopental decreased cGMP concentrations without altering nitric oxide formation clearly indicates that this anaesthetic decreases GC activity or augments cGMP breakdown in iNOS-expressed vascular smooth muscle. In spite of a marked decrease in cGMP concentration, thiopental at the concentrations tested (which were higher than clinically relevant concentrations[6]) did not alter the tension of iNOS-induced vascular smooth muscle. This may be because thiopental, at these concentrations, has vasodilator effects, mainly as a result of suppression of calcium sensitivity of vascular smooth muscle.[6] Thus our study failed to show that thiopental ameliorated vascular collapse caused by activation of iNOS. However, as anaesthetic management is mandatory in some septic cases and almost all anaesthetics have vasodilator effects, thiopental may be still more beneficial than other anaesthetics in some septic cases.

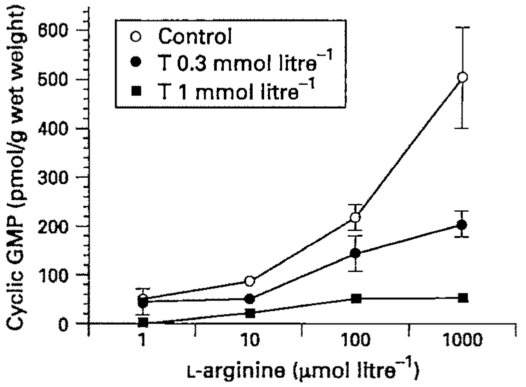

Figure 1 Modification of cGMP concentrations by thiopental in LPS-treated aortic rings. After LPS treatment, some rings were untreated (control) or treated with thiopental (T) 0.3 or 1 mmol litre^{-1} for 10 min, and then some rings were exposed to L-arginine 1 μmol litre^{-1} to 1 mmol litre^{-1} for 12 min. The rings were quickly frozen in liquid nitrogen, homogenized in 6% v/v trichloroacetic acid and subjected to ether extraction and succinylation. cGMP in each sample was assessed by radioimmunoassay using a Yamasa cGMP assay kit (Yamasa Shoyu Co., Chiba, Japan). *n*=5–7 each.

References

1. Zuo Z, Tichotsky A, Johns RA. Halothane and isoflurane inhibit vasodilatation due to constitutive but not inducible nitric oxide synthase. Implications for the site of anesthetic inhibition of the nitric oxide/guanylyl cyclase signaling pathway. *Anesthesiology* 1996; **84**: 1156–1165.
2. Kessler P, Kronemann N, Hecker M, Busse R, Schini-Kerth VB. Effects of barbiturates on the expression of the inducible nitric oxide synthase in vascular smooth muscle. *Journal of Cardiovascular Pharmacology* 1997; **30**: 802–810.
3. Terasako K, Nakamura K, Toda H, Kakuyama M, Hatano Y, Mori K. Barbiturates inhibit endothelium-dependent and independent relaxations mediated by cyclic GMP. *Anesthesia and Analgesia* 1994; **78**: 823–830.
4. Terasako K, Nakamura K, Miyawaki I, Toda H, Kakuyama M, Mori K. Inhibitory effects of anesthetics on cyclic guanosine monophosphate (cGMP) accumulation in rat cerebellar slices. *Anesthesia and Analgesia* 1994; **79**: 921–926.
5. Gilliam MB, Sherman MP, Griscavage JM, Ignarro LJ. A spectrophotometric assay for nitrate using NADPH oxidation by Aspergillus nitrate reductase. *Annals of Biochemistry* 1993; **212**: 359–365.
6. Kitamura R, Kakuyama M, Nakamura K, Miyawaki I, Mori K. Thiobarbitones suppress depolarization-induced contraction of vascular smooth muscle without suppression of calcium influx. *British Journal of Anaesthesia* 1996; **77**: 503–507.

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Patient-controlled interscalene analgesia with ropivacaine after major shoulder surgery: PCIA *vs* PCA

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Summary

We have compared the efficacy of patient-controlled interscalene analgesia (PCIA) using ropivacaine with patient-controlled analgesia (PCA) using nicomorphine in 60 patients (n=30 in each group), in a prospective, randomized study. In both groups, all patients received interscalene block with 0.75% ropivacaine before induction of anaesthesia. Six hours after interscalene block, patients in group PCIA received continuous infusion of 0.2% ropivacaine at a rate of 5 ml h^{-1} with a bolus dose of 3 or 4 ml and a lockout time of 20 min; patients in group PCA received continuous infusion of nicomorphine 0.5 mg h^{-1} and a bolus dose of 2 or 3 mg with a lockout time of 20 min. Control of pain was significantly better from 12 to 48 h after operation (except at 42 h) in group PCIA. Nausea and pruritus occurred significantly more frequently in group PCA. Patient satisfaction was greater in group PCIA. We conclude that the use of 0.2% ropivacaine using PCIA was an efficient way of managing pain after major shoulder surgery and compared favourably with PCA nicomorphine in terms of pain relief, side effects and patient satisfaction. (*Br. J. Anaesth.* 1998; **81**: 603–605).

Keywords: anaesthetics local, ropivacaine; analgesics opioid, nicomorphine; analgesia, patient-controlled; surgery, orthopaedic

Severe postoperative pain, particularly within the first 48 h after operation, is frequently observed after major shoulder surgery.[1] Adequate management of pain after surgery is important, not only to improve the patient's well being, but also to facilitate recovery.

Interscalene block is a recognized effective means of providing anaesthesia–analgesia for shoulder surgery.[2] Use of long-acting local anaesthetics provides prolonged postoperative analgesia and reduces the need for opioids and the incidence of associated side effects. Recently, we have shown that patient-controlled interscalene analgesia (PCIA) with bupivacaine was superior to patient-controlled analgesia (PCA) with nicomorphine in the management of postoperative pain after major shoulder surgery.[3] Ropivacaine has less cardiotoxicity and a greater degree of separation between motor and sensory block compared with bupivacaine.[4] To our knowledge, there are no studies on continuous infusion of ropivacaine and major shoulder surgery. In this study, we have assessed and compared the efficacy of PCIA with ropivacaine and PCA with nicomorphine after shoulder arthroplasty or rotator cuff repair.

Methods and results

After obtaining approval from the Institutional Ethics Committee and written informed consent, we studied prospectively 65 adults of both sexes, ASA I or II, aged 18–75yr, weighing 50–100 kg, undergoing elective shoulder arthroplasty or rotator cuff repair. Exclusion criteria were contraindications to interscalene block, including severe bronchopulmonary disease, known allergy to ropivacaine or opioids, prior analgesic treatments with opioids and pain in the shoulder as a result of other pathologies. Patients were allocated randomly to one of two groups (PCIA or PCA) according to a computerized randomization list. All patients had an interscalene block performed before induction of general anaesthesia. In both groups, the interscalene brachial plexus was identified using a nerve stimulator (Stimuplex, DIG, B. Braun Melsungen AG, Melsungen, Germany) connected to the proximal end of the metal inner needle of a plastic cannula (Contiplex, B. Braun Melsungen AG, Melsungen, Germany). Placement of the needle was considered successful when a group of muscles distal to the deltoid was stimulated with a threshold stimulation of less than 0.5 mA.

In both groups, interscalene block was performed with 0.75% ropivacaine (Naropin) 30 ml. In the PCIA group, a catheter (Contiplex, od 0.85 mm) was introduced distally within the interscalene sheath for up to 7–8 cm and fixed to the skin with adhesive tapes. In this group, interscalene block was performed by administering ropivacaine through the catheter, after it was placed within the interscalene sheath. In the PCA group, interscalene block was performed by administering ropivacaine when the stimulation needle was adequately placed. Interscalene block was confirmed in all patients by sensory (inability to recognize cold temperature) and motor (inability to extend the arm) block involving the radial and median nerves, within 20 min after administration of the local anaesthetic.

General anaesthesia was similar for all patients. Patients were premedicated with midazolam 0.1 mg kg^{-1} orally, 1 h before anaesthesia. After completion of interscalene block, anaesthesia was induced with propofol 1.5–2 mg kg^{-1} and maintained with propofol 8–10 mg kg^{-1} h^{-1}. Tracheal intubation was facilitated with rocuronium 0.8 mg kg^{-1}, and fentanyl 2–3 μg kg^{-1}

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was given within the first 20 min after induction. For all patients, infusion of either ropivacaine via the interscalene catheter or i.v. nicomorphine was started in the recovery room, 6 h after the initial interscalene block.

Group PCIA (Pain Management Provider/Abbott Lab., North Chicago, IL, USA) received continuous infusion of 0.2% ropivacaine at a rate of 5 ml h^{-1} and a bolus dose of 4 ml (8 mg) for patients >65 kg and 3 ml (6 mg) for patients <65 kg, with a lockout time of 20 min, via the interscalene catheter. At the same time, group PCA (Pain Management Provider/Abbott Lab.) received continuous infusion of nicomorphine 0.5 mg h^{-1} and a bolus dose of 3 mg for patients >65 kg and 2 mg for patients <65kg, with a lockout time of 20 min. The study was ended 48 h after the initial interscalene block. If pain was not controlled adequately (pain score >40 on the visual analogue scale), patients received paracetamol 1 g i.v. to a maximum dose of 6 g per day.

A research nurse, not involved in the intraoperative part of the study, was responsible for asking the patient about pain scores, appearance of side effects, patient satisfaction and recording technical problems associated with PCA or PCIA pumps. Pain was assessed using a visual analogue scale, from 0=no pain to 100=worst pain imaginable, at the time interscalene block was performed (*t*=0), at the beginning of PCIA or PCA (*t*=6) and every 6 h for the next 42 h.

The incidence of nausea, vomiting, pruritus or other side effects was noted. The time of the first PCIA or PCA was checked, in addition to the number of paracetamol supplements needed. Nausea and pruritus were recorded only when patients asked for treatment. Nausea and vomiting were treated by tropisetron 2 mg i.v. and pruritus by propofol 10 or 20 mg i.v., repeated as necessary.[5]

Motor block was considered present when the patient complained of difficulties in flexing or extending any of the fingers, 12 h after interscalene block. Patient satisfaction, assessed 6 h after the end of the study, was evaluated using a visual analogue scale, from 0=not satisfied to 10=entirely satisfied.

Results are reported as mean (SD). Patient data were compared using one-way analysis of variance, pain score (VAS) by the Mann–Whitney test with Bonferroni's correction for multiple comparisons, patient satisfaction, time of first bolus and paracetamol supplements by the Mann–Whitney test, and side effects with Fisher's exact test. For all determinations, $P<0.05$ was considered significant.

The two groups were comparable in patient characteristics and surgical data. Five patients were excluded from the study: three in group PCIA and two in group PCA. In two patients in group PCIA, the interscalene catheter was accidentally pulled out while in the other, insertion of the catheter within the interscalene sheath could not be achieved. In group PCA, one patient was withdrawn after 18 h because of intractable vomiting secondary to nicomorphine while the other asked to be withdrawn from the study after 30 h as he felt dizzy every time he pushed the PCA switch. The time of the first PCIA or PCA bolus was similar in both groups. There was no significant difference between groups in the mean dose of supplementary paracetamol (table 1).

Table 1 Side effects and analgesic requirements in the two groups. Number (*n*) of patients or mean (SD). $^*P<0.05$

	PCIA group	PCA group
Nausea (*n*)	3*	14
Vomiting (*n*)	2	8
Pruritus (*n*)	0*	8
Motor block (*n*)	6	4
Time of first bolus (min)	930 (444)	786 (276)
Paracetamol supplement (g)	2.1 (3.3)	3.5 (3.4)
Patient satisfaction	9.6 (0.7)*	7.5 (2.4)
Range	(7–10)	(2–10)

Pain scores were similar in both groups at the time the interscalene block was performed (*t*=0) and when PCIA and PCA was started (*t*=6). Except for 42 h after operation, pain scores were significantly decreased at all times (12,18, 24, 30, 36 and 48 h) ($P<0.05$) (fig. 1).

Side effects during the study are summarized in table 1. Nausea and pruritus were observed less frequently in group PCIA ($P<0.05$). Vomiting was less frequent in group PCIA (ns). Motor block was comparable in both groups.

Patient satisfaction was significantly greater in the PCIA group ($P<0.05$) (table 1).

Comment

We have shown that 0.2% ropivacaine via an interscalene catheter provided efficient control of postoperative pain after major shoulder surgery, and was associated with a low incidence of side effects and high patient satisfaction.

Continuous infusion of ropivacaine 10 mg h^{-1} was chosen, as according to pharmacodynamic differences,[6] this dose may be considered equivalent to bupivacaine 7.5 mg h^{-1}, which was satisfactory in our previous study.[3] A background infusion was used as patients showed a high degree of satisfaction in our first study.[3] The dose of nicomorphine was unchanged from our previous investigation as we observed a favourable ratio between analgesic treatment and side effects.[3] A background infusion of nicomorphine was also given to avoid methodological bias, knowing that PCA with a concurrent infusion did not show any advantages compared with PCA alone.[7] Study duration was limited to the first 48 h after operation, as it was well demonstrated that after major shoulder

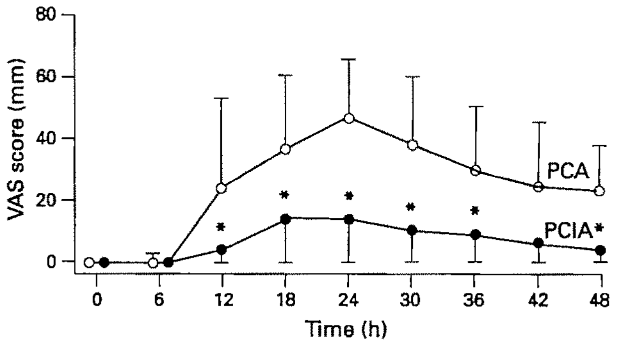

Figure 1 Pain assessment by visual analogue scale (VAS, 0–100 mm) (mean, SD) in the patient-controlled analgesia (PCA) and patient-controlled interscalene analgesia (PCIA) groups ($^*P<0.05$).

surgery, the most severe pain occurred within this time interval.

Clinical experience with ropivacaine and peripheral block is still limited. Nolte, Fruhstrorfer and Edstrom[8] demonstrated in a dose–response study in human volunteers undergoing bilateral nerve block that ropivacaine was maximally effective at concentrations of 0.5–0.75%, with a profile of action similar to bupivacaine. This is in accordance with our initial bolus of 0.75% ropivacaine. Hickey and colleagues[9] compared the effectiveness of 0.25% ropivacaine and 0.25% bupivacaine in patients receiving interscalene block for upper extremity surgery and found that both drugs were inadequate for this type of surgery. The same authors, using the same technique, investigated the efficacy of 0.5% ropivacaine with or without epinephrine (adrenaline) for shoulder surgery.[10] They found that 0.5% ropivacaine, even without epinephrine, provided excellent sensory and motor block of prolonged duration in 87% of patients. This is slightly lower than the incidence observed in our study (100%) but may be explained by the higher concentration (0.75%) used in our study.

In group PCA, VAS satisfaction was 7.5; this value is similar to that found in our previous study.[6,7] Difference in the scale used and type of surgery may explain the slightly lower value reported in our study compared with that found in the literature (90–95%).[11] The incidence of vomiting (27%) was comparable with the 25% found in the first study[3] and is within the usual range of the incidence of vomiting after general anaesthesia and PCA.[7] The incidence of pruritus (25%) was also comparable with previous work.[3] In the PCIA group, VAS satisfaction was 9.6. This value is similar to that reported after bupivacaine using a similar protocol.[3]

The study design may be criticized by the unblinded nature of the study. In order to minimize this bias, a nurse in the pain clinic, not involved in the study or informed directly about its aims, was asked to collect the data.

In summary, we have demonstrated the efficacy of continuous infusion of 0.2% ropivacaine using a PCIA technique to manage pain after major shoulder surgery. PCIA with ropivacaine compared favourably with PCA nicomorphine in this clinical setting in terms of quality of analgesia, side effects and patient satisfaction. In view of the lesser potential for toxicity and its pharmacokinetic properties, ropivacaine may be an advantageous and safer alternative to bupivacaine to provide analgesia.

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References

1. Tuominen M, Pitkanen M, Rosenberg PH. Postoperative pain relief and bupivacaine plasma levels during continuous interscalene brachial plexus block. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 276–278.
2. Brown AR, Weiss R, Greenberg C, Flatow EL, Bigliani LU. Interscalene block for shoulder arthroscopy: comparison with general anesthesia. *Arthroscopy* 1993; **9**: 295–300.
3. Borgeat A, Schappi B, Biasca N, Gerber C. Patient-controlled analgesia after major shoulder surgery: PCIA versus PCA. *Anesthesiology* 1997; **87**: 1343–1347.
4. Markham A, Faulds D. Ropivacaine—A review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs* 1996; **52**: 429–449.
5. Borgeat A, Wilder-Smith OHG, Saiah M, Rifat K. Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology* 1992; **76**: 510–512.
6. Wood MB, Rubin AP A comparison of epidural 1% ropivacaine and 0.75% bupivacaine for lower abdominal gynecologic surgery. *Anesthesia and Analgesia* 1993; **76**: 1274–1278.
7. Hecker BR, Albert L. Patient-controlled analgesia: A randomized, prospective comparison between two commercially available PCA pumps and conventional analgesic therapy for postoperative pain. *Pain* 1988, **35**: 115–120.
8. Nolte H, Fruhstorfer H, Edstrom HH. Local anesthetic efficacy of ropivacaine (LEA 103) in ulnar nerve block. *Regional Anesthesia* 1990; **15**: 118–124.
9. Hickey R, Rowley CL, Candido KD, Hoffman J, Ramamurthy S, Winnie AP. A comparative study of 0.25% ropivacaine and 0.25% bupivacaine for brachial plexus block. *Anesthesia and Analgesia* 1992; **75**: 602–606.
10. Hickey R, Candido KD, Ramamurthy S, Winnie AP, Blanchard J, Raza SM, Hoffmann J, Durrani Z, Masters RW Brachial plexus block with a new local anaesthetic: 0.5 per cent ropivacaine. *Canadian Jounal of Anaesthesia* 1990; **37**: 732–738.
11. Ellis R, Haines D, Shah R, Cotton BR, Smith G. Pain relief after abdominal surgery—a comparison of i.m morphine, sublingual buprenorphine and self-administered i.v. pethidine. *British Journal of Anaesthesia* 1982; **54**: 421–428.

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Remifentanil prevents an increase in intraocular pressure after succinylcholine and tracheal intubation†

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Summary

We have studied changes in intraocular pressure (IOP) in 30 patients after succinylcholine (suxamethonium) and tracheal intubation following administration of propofol 2 mg kg^{-1} and either remifentanil 1 μg kg^{-1} (group R) or saline (group S). IOP was measured before induction, before administration of succinylcholine and the study drug, before intubation and for every 1 min after intubation for 5 min. There was a significant decrease in IOP in group R compared with group S from the time of administration of the study drugs to the end of the study ($P<0.006$). (*Br. J. Anaesth.* 1998; **81**: 606–607).

Keywords: eye, intraocular pressure; analgesics opioid, remifentanil; neuromuscular block, succinylcholine

Remifentanil is a new, ultra-short acting, selective, mu-receptor agonist which is 20–30 times more potent than alfentanil.[1] Its ester linkage renders it susceptible to hydrolysis by blood and tissue non-specific esterases resulting in a short terminal half-time of less than 10 min at the site of action.

Succinylcholine (suxamethonium) is used to facilitate rapid tracheal intubation in patients who are at risk of aspiration of gastric contents. However, administration of succinylcholine and tracheal intubation are associated with an increase in intraocular pressure (IOP).[2] Alfentanil 10 μg kg^{-1} attenuates this increase in IOP[3] but may be associated with respiratory depression, especially in an elderly population. Remifentanil has a therapeutic profile that may make it a suitable alternative to alfentanil; it has a rapid onset (time to peak effect 60–70 s), is metabolized rapidly, and therefore respiratory depression should be short-lived.

We have studied the efficacy of remifentanil in preventing an increase in IOP after administration of succinylcholine and tracheal intubation in a double-blind, randomized study.

Methods and results

After obtaining approval from our Institutional Review Board and written, informed consent, we studied 34 patients (ASA I or II) undergoing elective eye surgery. Exclusion criteria included a history of glaucoma, oesophageal reflux or hiatus hernia, allergies to any of the study drugs and administration of sedative or opioid drugs in the previous 24 h.

Patients were allocated randomly to one of two groups: group R received remifentanil 1 μg kg^{-1} diluted to 5 ml with normal saline and group S received normal saline 5 ml. Patients were premedicated with midazolam 0.03 mg kg^{-1} i.v., 10 min before anaesthesia. Monitoring of ECG, heart rate (HR), peripheral arterial haemoglobin oxygen saturation (Sp_{O_2}) and mean arterial pressure (MAP) was commenced. Tetracaine 0.5% drops were administered to the non-operated eye and IOP was measured using an applanation tonometer (Tono-Pen XL, Mentor O&O, Inc. Norwell, MA, USA) (time 1).

After 3 min of preoxygenation, anaesthesia was induced with propofol 2 mg kg^{-1} at an infusion rate of 40 mg every 10 s. MAP, HR and IOP were measured after loss of consciousness (time 2) and succinylcholine 1 mg kg^{-1} was administered followed by the study drug, given as a bolus. At 60 s, measurements were repeated and laryngoscopy and tracheal intubation performed (time 3). Further measurements of MAP, HR and IOP were obtained every 1 min after tracheal intubation for 5 min (times 4–8). The anaesthetist performing the intubation and the surgeon measuring IOP were unaware of which study drug had been administered. Anaesthesia was maintained with 1% isoflurane and 66% nitrous oxide in oxygen, and the lungs were ventilated to normocapnia. There was no further stimulation of the patient during the study.

Wilcoxon two-sample rank sum test was used to compare patient data and MAP, HR and IOP at each time. Bonferroni correction was applied for multiple comparisons resulting in a significance level of 0.006. Repeated measures ANOVA was used to compare times 2–8 with time 1. $P<0.0035$ was considered statistically significant using Bonferroni correction. Randomization of patients was achieved using a computer-generated table.

We studied 15 patients in each group. Four patients were excluded for coughing or gagging during the 5-min period after intubation. There were no differences between groups in patient data. Mean age and weight in groups S and R were 59.5 (range 33–75) yr and 58.6 (31–78) yr, and 72.8 (SD 12.3) kg and 73.2 (11.9) kg. The number of males in each group was 10 and nine, respectively.

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Table 1 Multiple comparisons of arterial pressure, heart rate (HR) and intraocular pressure (IOP) at times 1–8 in group S (n=15) and group R (n=15) (mean (SD) [range]). Time 1 = before induction, 2 = before study drug, 3 = before intubation, 4–8 = every 1 min after intubation for 5 min. *P<0.006

	Time							
	1	2	3	4	5	6	7	8
MAP (mm Hg)								
Group S	97 (13)	80 (15)	96 (22)*	123 (23)*	117 (20)*	113 (21)*	103 (16)*	100 (16)*
	[76–115]	[51–108]	[73–142]	[76–166]	[78–136]	[73–137]	[75–138]	[73–131]
Group R	97 (17)	86 (23)	71 (23)	75 (29)	71 (26)	68 (23)	67 (22)	67 (20)
	[70–139]	[62–136]	[52–116]	[49–138]	[45–138]	[46–138]	[48–136]	[48–125]
HR (beat min^{-1})								
Group S	68 (11)	71 (10)	78 (10)	91 (15)*	87 (13)*	85 (13)*	81 (14)	79 (14)
	[49–85]	[48–87]	[63–98]	[69–119]	[64–111]	[64–108]	[55–107]	[60–106]
Group R	72 (12)	77 (13)	72 (19)	71 (19)	69 (16)	68 (16)	67 (15)	66 (13)
	[54–90]	[56–102]	[46–86]	[44–88]	[45–85]	[42–84]	[40–82]	[40–87]
IOP (mm Hg)								
Group S	16.4 (3.1)	11.7 (3.4)	16.5 (3.2)*	24.2 (4.5)*	23.7 (5.6)*	21.6 (4.5)*	20.4 (4.6)*	18.7 (4.9)*
	[9–21]	[6–16]	[9–22]	[18–35]	[17–35]	[14–33]	[14–33]	[14–32]
Group R	17.1 (3.2)	12.1 (2.6)	13 (2.8)	12.7 (2.6)	12.7 (2.8)	12.4 (2.5)	11.9 (2.5)	11.1 (2.2)
	[12–23]	[8–16]	[8–17]	[9–16]	[9–18]	[8–16]	[8–17]	[6–14]

There was a significant decrease in MAP in group R from times 2–8 compared with time 1 (baseline) but only at time 2 in group S (P<0.003). After intubation, MAP increased significantly compared with baseline in group S at times 4–5. There was no difference in HR in group R at times 2–8 compared with baseline but there was an increase in group S from times 4–8 (P<0.003). There was a significant decrease in IOP in group R at times 2–8 and an increase in group S at times 3–6 compared with time 1 (P<0.003). There was a significant difference in IOP in group R compared with group S from times 3–8 (P<0.006) (table 1).

Comment

Our results showed an increase in IOP above baseline in group S with administration of succinylcholine and tracheal intubation. This was associated with an increase in MAP and HR after the haemodynamic response to laryngoscopy and tracheal intubation. Remifentanil 1 µg kg^{-1} blunted this response, with no significant change in IOP after induction of anaesthesia (table 1).

The use of succinylcholine is controversial in patients with penetrating eye injuries. The increase in IOP after administration of succinylcholine may depend on the timing and dose of the drug, special tonic response of the Felderstruktur fibres in the extraocular muscles or a direct effect of succinylcholine on choroidal blood volume or aqueous humour formation.[4] The risk of vitreous expulsion as a result of increased IOP needs to be balanced against the risk of aspiration of gastric contents. However, previous studies have shown that laryngoscopy and intubation are associated with a greater increase in IOP than succinylcholine.[2]

Normal IOP ranges from 15 to 20 mm Hg. The mechanisms by which opioids may decrease IOP include relaxation of the intra- or extraocular muscles, and facilitation of outflow or a decrease in production of aqueous humour.[5] Remifentanil, administered as an infusion to provide sedation for ophthalmic surgery, was associated with a significant decrease in IOP compared with alfentanil.[6]

Remifentanil 1 µg kg^{-1} produced a maximum decrease in IOP within 1 min after injection. Therefore, it may be administered at the same time as the induction agent during rapid sequence induction to facilitate smooth laryngoscopy and intubation of the trachea, in addition to preventing the hypertensive response and increase in IOP. However, remifentanil has a short duration of action. Other opioids or neuromuscular blocking agents may need to be administered to prevent coughing which can also result in an increase in IOP when the effects of succinylcholine wear off.

In summary, we conclude that administration of remifentanil 1 µg kg^{-1} after induction of anaesthesia with propofol 2 mg kg^{-1} prevented an increase in IOP associated with administration of succinylcholine and tracheal intubation.

References

1. Glass PS, Hardman D, Kamiyama Y. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (G187084B). *Anesthesia and Analgesia* 1993, 77. 1031–1040.
2. Mirakhur RK, Shepherd WFI, Darrah WC Propofol or thiopentone· effects on intraocular pressure associated with induction of anaesthesia and tracheal intubation (facilitated with suxamethonium). *British Journal of Anaesthesia* 1987; 59 431–436.
3. Mostafa SM, Lockhart A, Kumar D, Bayoumi M Comparison of effects of fentanyl and alfentanil on intraocular pressure. *Anaesthesia* 1986; 41: 493–498.
4. Cook JH. The effect of succinylcholine on intraocular pressure. *Anaesthesia* 1981; 36: 359–365.
5. Duncalf D, Foldes FF. Effect of anaesthetic drugs and muscle relaxants on intraocular pressure. *International Ophthalmology Clinics* 1973; 13: 21–33.
6. Sung YF, Stulting RD, Beatie CD, Stead S, Jamerson BD, Roland CL. Intraocular pressure effects of remifentanil (GI87084B) and alfentanil. *Anesthesiology* 1994; 81: A35

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Airway control during percutaneous dilatational tracheostomy: pilot study with the intubating laryngeal mask airway

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Summary

Percutaneous dilatation tracheostomy has become a common procedure for bedside insertion of tracheostomy tubes in the intensive care unit. Management of the airway during the procedure using the laryngeal mask airway (LMA) and other methods has been described. The intubating laryngeal mask airway has several potential benefits for airway management during percutaneous dilatation tracheostomy compared with the LMA. These include the use of both the fibreoptic bronchoscope and tracheal tube if necessary. We report the results of a pilot study of 10 patients that illustrates these advantages. (*Br. J. Anaesth.* 1998; **81**: 608–609)

Keywords: airway, management; equipment, masks anaesthesia; intubation tracheal; surgery, tracheostomy

Percutaneous dilatational tracheostomy is a widely used alternative to formal surgical tracheostomy in the intensive care unit (ICU). It involves insertion of a needle and guidewire into the trachea followed by progressive dilatation of the resultant tract and placement of a tracheostomy tube. Before insertion of the needle into the trachea, the cuff of the tracheal tube is deflated and withdrawn so that the cuff is just seen at the vocal cords on direct laryngoscopy. Failure to correctly position the tracheal tube may result in cuff puncture, tube transection by the needle or accidental extubation, leading to loss of the airway. There are also problems resulting from the anaesthetist and operator competing for access to the patient's airway. The use of the laryngeal mask airway (LMA) during percutaneous dilatational tracheostomy avoids some of these difficulties.[1] However, there remains the possibility of aspiration of gastric contents, while re-intubation via the LMA is limited by difficulty in aligning the LMA inlet with the larynx and the need to use a small (6.0 mm) tracheal tube.

Recently, the intubating LMA has been introduced into clinical practice as a ventilatory device and blind intubation guide.[2 3] The intubating LMA consists of an anatomically curved, short, wide-bore stainless steel tube sheathed in silicone which is bonded to a laryngeal mask cuff and a guiding handle. Sizes 3, 4 and 5 are available, which can accommodate 8-mm, 8.5-mm and 9-mm tracheal tubes, respectively. We postulated that the intubating LMA could be used as an airway on its own during percutaneous dilatational tracheostomy. This would allow safe withdrawal and reinsertion of a tracheal tube if required and could be used as a conduit for the passage of a fibreoptic bronchoscope without interrupting intermittent positive pressure ventilation (IPPV).

Methods and results

Informed consent was obtained from relatives of 10 patients undergoing elective percutaneous dilatational tracheostomy. All patients had been "fasted" for 4–6 h before the procedure and were receiving standard monitoring, including pulse oximetry and invasive arterial pressure measurements. Monitoring of intracranial pressure was performed in two patients. All patients were sedated by infusion of propofol and alfentanil and the infusion rates were increased until patients were suitably anaesthetized; neuromuscular block was produced with atracurium 0.5 mg kg^{-1}.

Thorough suctioning of the oropharynx and nasogastric tube was performed and inspired oxygen increased to 100%. A deflated intubating LMA (size 4 for females, size 5 for males) was inserted behind the tracheal tube using the recommended technique and the cuff of the intubating LMA inflated to a pressure of 60 cm H_2O. The cuff of the tracheal tube was then deflated and the tracheal tube removed. IPPV was continued initially by connecting the ventilator breathing system directly to the intubating LMA. Manipulation of the intubating LMA handle allows air leaks around the cuff to be minimized during IPPV. If ventilation was satisfactory, as judged by adequate chest movement, minimal air leak and stable vital signs, percutaneous dilatational tracheostomy proceeded with the intubating LMA alone. Percutaneous dilatational tracheostomy was performed using the Cook system (Cook Critical Care Systems, USA) in all patients. If IPPV was not wholly satisfactory with the intubating LMA alone, then a 7.0-, 7.5- or 8.0-mm reinforced straight silicone tracheal tube with a proprietary tip (Euromedical, Malaysia) was introduced via the intubating LMA with fibreoptic bronchoscope guidance to position the tip of the tracheal tube just below the vocal cords. Correct siting and function of the tracheostomy tube were confirmed by chest x-ray in all patients.

Comment

Patients requiring respiratory support usually have a tracheal tube to secure the airway in the first instance.

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Table 1 Patient characteristics and ventilatory variables. PSV = Pressure support ventilation, SIMV = synchronized intermittent mandatory ventilation, PCIRV = pressure controlled inverse ratio ventilation. * Peak pressure not recorded

Patient No.	Diagnosis	Sex (F/M)	Age (yr)	No. ICU days	COETT (mm)	F_{IO_2}	Pressure (cm H_2O)	SIMV (min)	I:E
1	Diverticular abscess plus sepsis	F	76	9	8.0	0.45	PSV/PEEP 15/5	0	1 2
2	ARDS following freshwater drowning	M	64	7	9.0	0.9	PCIRV/PEEP 20/8	12	2:1
3	Septic complications and IDDM	F	66	23	8.0	0.35	PSV/PEEP 12/5		1.2
4	Head injury and cerebral oedema	M	22	9	9.0	0.4	SIMV 20/0	10	1:2
5	Abdominal sepsis and respiratory failure	F	72	7	8.0	0.5	PSV/PEEP 15/5	10	1:2
6	Multiorgan failure	F	66	8	8.0	0.5	PSV/PEEP 20/5	0	1:2
7	Meningococcal sepsis	M	39	10	9.0	0.6	SIMV/PEEP */12	12	1.2
8	Multiple trauma with head injury	M	50	8	9.0	0.6	SIMV/PEEP */7	12	1.2
9	Multiorgan failure	F	60	11	8.0	0.55	SIMV/PEEP */6.5	10	1:2
10	Multiorgan failure	M	64	8	9.0	0.5	SIMV/PEEP */6.5	12	1:2

If prolonged ventilatory support is anticipated, a tracheostomy is often considered. There is no agreement as to the optimal time for conversion from translaryngeal intubation to tracheostomy.[4] Our preferred technique for tracheostomy is percutaneous dilatational tracheostomy undertaken at the bedside.

The incidence of perioperative complications in prospective studies of percutaneous dilatational tracheostomy is approximately 10%[4] and these include bleeding, surgical emphysema, pneumothorax, incorrect placement of tracheal cannulae or dilators, or both, leading to a variety of immediate and long-term complications.[5] Various methods of airway control during percutaneous dilatational tracheostomy have been practised, including withdrawal of the tracheal tube until the cuff lies at the level of the vocal cords, but this technique predisposes to problems of the shared airway and accidental extubation. The LMA has been used to overcome some of the problems associated with the tracheal tube, especially that of the shared airway.[1] The standard LMA is used successfully as a conduit for blind and fibreoptic bronchoscope-assisted intubation, but unlike the intubating LMA, was not specifically designed for this purpose.[3] The intubating LMA has a shorter, wider tube, facilitates easy passage of a fibreoptic bronchoscope or a larger sized tracheal tube and overcomes the diameter–length limitations for tracheal tube placement imposed by the standard LMA. Neither the LMA nor the intubating LMA prevent aspiration, but nor does a tracheal tube with a deflated cuff.

Recently, the Combitube has been used for airway management during percutaneous dilatational tracheostomy in ICU patients.[6] This technique precludes the use of a fibreoptic bronchoscope to identify tracheal structures and needle placement, as the Combitube tends to lie in the oesophagus. Additionally, antero-lateral displacement of the trachea on inflation of the distal cuff may be an added hazard to the blind procedure of needle insertion into the trachea. A re-designed Combitube, which allows bronchoscopy, has been described but is not commercially available.[7]

Our preliminary unblinded study (table 1) showed that the intubating LMA was an effective and successful ventilatory device in all 10 patients. The intubating LMA does not require head–neck manipulation for insertion, thus proving invaluable in airway control of head injury–trauma patients where cervical spine pathology is present or suspected. There is improved ventilating ability by manipulating the device using the metal handle and it was used as the sole airway after removal of the tracheal tube in all of our patients. The dedicated tracheal tube facilitates immediate intubation either blindly or with fibreoptic bronchoscope guidance, thus providing the ability to continuously control the airway. Finally, a fibreoptic bronchoscope could be used in conjunction with the intubating LMA for trans-illumination of the trachea to facilitate accurate positioning of the needle into the trachea. Larger multicentre studies are needed to confirm these findings.

References

1. Dexter TJ. The laryngeal mask airway: a method to improve visualisation of the trachea and larynx during fibreoptic assisted percutaneous tracheostomy *Anaesthesia and Intensive Care* 1994; 22: 35–39.
2. Brain AIJ, Verghese C, Addy EV, Kapila A, Brimacombe J. The intubating laryngeal mask. II: a preliminary clinical report of a new means of intubating the trachea. *British Journal of Anaesthesia* 1997; 79· 704–709.
3. Kapila A, Addy EV, Verghese C, Brain AIJ. The intubating laryngeal mask airway: an initial assessment of performance. *British Journal of Anaesthesia* 1997; 79: 710–713.
4. El-Naggar M, Sadagopan S, Levine H, Kantor H, Collins VJ. Factors influencing choice between tracheostomy and prolonged translaryngeal intubation in acute respiratory failure; a prospective study. *Anesthesia and Analgesia* 1976, 55: 195–201.
5. Van Heurn LWE, Theunissen PHMH, Ramsay G, Brink PRG. Pathologic changes of the trachea after percutaneous dilatational tracheostomy. *Chest* 1996; 109. 1466–1469.
6. Mallick A, Quinn AC, Bodenham AR, Vucevic M. Use of the Combitube for airway maintenance during percutaneous dilatational tracheostomy. *Anaesthesia* 1998; 53: 249–255.
7. Krafft P, Roggla M, Fridrich P, Locker GJ, Frass M, Benumof JL. Bronchoscopy via a re-designed Combitube in the esophageal position. *Anesthesiology* 1997, 86: 1041–1045

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The intubating laryngeal mask airway (ILMA): initial experience in Singapore

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Summary

We have evaluated the intubating laryngeal mask airway (ILMA) for ventilation and for blind tracheal intubation. After induction of anaesthesia with fentanyl 1 μg kg^{-1} and propofol 3 ml kg^{-1}, the ILMA was placed successfully on the first attempt in all 100 patients. After administration of atracurium 0.5 mg kg^{-1}, blind tracheal intubation was successful in 97% of patients—50% on the first attempt, 42% on the second and 5% on the third. Success was improved by pulling the metal handle of the ILMA towards the intubator in an "extension" manoeuvre, if intubation was not possible on the first attempt. These findings confirm the effectiveness of the ILMA in an Asian population. (*Br. J. Anaesth.* 1998; **81**: 610–611).

Keywords: equipment, masks anaesthesia; intubation tracheal; intubation tracheal, technique

The difficult airway is still a significant cause of morbidity and mortality despite a plethora of aids to tracheal intubation. The laryngeal mask airway (LMA) has found a place in this arena[1] and has been developed further as a means of tracheal intubation—the intubating laryngeal mask airway (ILMA).[2] We describe the use of the ILMA and a preliminary assessment of its performance in an Asian group of patients.

Methods and results

After obtaining Ethics Committee approval and informed consent, we studied ASA I and II patients presenting for elective surgery. Exclusion criteria were a history of gastro-oesophageal reflux, severe obesity and inadequate fasting. After preoxygenation, anaesthesia was induced with fentanyl 1 μg kg^{-1} and propofol 3 mg kg^{-1}. The patients' lungs were ventilated with 100% oxygen supplemented with 2% isoflurane by face mask until the onset of neuromuscular block produced with atracurium 0.5 mg kg^{-1} i.v. Direct laryngoscopy was performed and the view of the larynx graded according to Cormack and Lehane.[3] After further manual ventilation, an ILMA was introduced (usually size 3 for women and size 4 for men, given the low weight of our population). Successful placement was judged by the ability to deliver a tidal volume of 8 ml kg^{-1} at a rate of 10 bpm, without leak, at an airway pressure $\leq$20 cm H_2O, and by a satisfactory capnograph tracing.

Blind tracheal intubation was attempted using a lubricated silicone tracheal tube (sizes 7 and 8 mm, respectively, for ILMA sizes 3 and 4) inserted into the metal tube of the ILMA. If the first attempt failed, subsequent attempts were performed with the metal handle of the ILMA pulled back towards the intubator. This "extension"[4] manoeuvre had been found previously to be useful in a pilot study in our patients. A maximum number of three attempts were allowed, the last with a "vertical lift" on the ILMA handle. Successful intubation was determined by capnography.

Five consultant anaesthetists studied 20 patients each. Eighty-six patients were Chinese, nine Malay, four Indian and one Caucasian. Eighty-four patients had a grade 1 larynx, 15 grade 2 and one grade 3. The five groups of patients were not significantly different in age, sex, weight or height. The ILMA was placed successfully in all patients on the first attempt. The overall success rate for intubation was 97%—50% on the first attempt, 42% on the second and 5% on the third. The anaesthetists varied in their success rates and the number of intubation attempts before successful intubation was carried out (table 1). The effect of experience on ease of intubation was not evident, as the two patients who's trachea could not be intubated by anaesthetist A were the seventh and 11th patients, while anaesthetist B failed to intubate the last patient. All three patients had a grade 1 larynx. In the one patient with a grade 3 larynx, intubation was successful on the first attempt. There was no morbidity associated with the ILMA.

Comment

This study was undertaken before the results of other studies[2,4,5] were published. The 100% success rate of establishing an effective airway with the ILMA on the first attempt, which supports the inclusion of the LMA in the ASA difficult airway algorithm,[1] was reproduced by our study. The overall 97% success rate for intubation was similar to those reported in two published series: 93% (n=100)[4] and 100% (n=150).[5] It is possible that our success rate may be improved by the use of further adjustments.[4] However, the use of the extension manoeuvre significantly improved the success rate, as reported previously.[4] Extension achieves a rotatory movement of the ILMA in the sagittal plane, and coupled with a vertical lift on the

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Table 1 Number (%) of patients in whom intubation was successful by each of five anaesthetists (A–E)

Anaesthetist	Successful at first attempt	Successful at second attempt	Successful at third attempt	Failed attempts
A	6 (30)	11 (55)	1 (5)	2 (10)
B	10 (50)	9 (45)	0	1 (5)
C	14 (70)	4 (20)	2 (10)	0
D	11 (55)	8 (40)	1 (5)	0
E	9 (45)	10 (50)	1 (5)	0

metal handle may improve alignment of the mask with an anterior larynx. We did not try the "flexion" manoeuvre, described by Kapila and colleagues,[4] who interestingly described deterioration in the fibreoptic view of the larynx in the majority of patients.

In summary, we have confirmed the value of the ILMA as a primary means of establishing an airway for blind tracheal intubation in a predominantly Chinese group of patients, whose airway characteristics such as smaller size, anterior larynx and retrognathia may differ from other populations.[6] The variability in performance of individual anaesthetists merits further study in larger numbers of patients.

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References

1. Benumof JL. Laryngeal mask airway and the ASA difficult airway algorithm. *Anesthesiology* 1996; 84: 686–699.
2. Brain AIJ, Verghese C, Addy EV, Kapila A. The intubating laryngeal mask. I: development of a new device for intubation of the trachea. *British Journal of Anaesthesia* 1997; 79: 699–703.
3. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; 39: 1105–1111.
4. Kapila A, Addy EV, Verghese C, Brain AIJ. The intubating laryngeal mask airway: an initial assessment of performance. *British Journal of Anaesthesia* 1997; 79: 710–713
5. Brain AIJ, Verghese C, Addy EV, Kapila A, Brimacombe J. The intubating laryngeal mask. II: a preliminary clinical report of a new means of intubating the trachea. *British Journal of Anaesthesia* 1997; 79: 704–709.
6. Butler PJ, Dhara SS. Prediction of difficult laryngoscopy: an assessment of the thyromental distance and Mallampati predictive tests. *Anaesthesia and Intensive Care* 1992; 20. 139–142.

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CASE REPORTS

Laryngotracheal separation after attempted hanging

S. DESHPANDE

Summary

The successful management of a 29-yr-old patient with tracheal separation between rings one and two after attempted hanging is described. Increasing difficulty with ventilation via a tracheal tube and surgical emphysema indicated the need for a tracheostomy. The diagnosis was made during the tracheostomy procedure when it was observed that the tracheal tube was protruding through the incomplete transection of the trachea such that Murphy's eye was aligned with the lower tracheal stump. The patient underwent primary anastomosis of the trachea with placement of a Lorenz tracheal stent. On subsequent follow-up he had evidence of damage to both recurrent laryngeal nerves. The signs and symptoms of laryngotracheal separation after blunt trauma are described. A review of the airway management has been made as it requires combined anaesthetic and surgical expertise. Injuries to the trachea may have severe, life-threatening consequences and early diagnosis and management reduce morbidity and mortality. (*Br. J. Anaesth.* 1998; **81**: 612–614).

Keywords: complications, laryngotracheal separation; airway, management; intubation tracheal

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Case report

A 29-yr-old male patient was transferred to our university hospital from a peripheral hospital for evaluation of laryngeal fracture. The patient had attempted to hang himself and was rescued by a witness within 2 min. On examination, he was conscious, had a hoarse voice, was coughing up blood and had stridor. Attempts, possibly to facilitate transfer, had been made to secure the airway by the paramedics at the site of the accident but were unsuccessful. Tracheal intubation was performed at the peripheral hospital under general anaesthetic using a 7.0-mm oral tracheal tube under fibreoptic vision. On examination of the larynx, the glottis appeared slit-like, there was significant oedema but no evidence of tears, disruption or bleeding. There was suspicion of a cervical spine injury and therefore he was placed in a cervical collar. CT scan performed at this hospital showed evidence of surgical emphysema with a displaced tracheal ring. Sedation, neuromuscular block and positive pressure ventilation were maintained during transfer to the university hospital.

On arrival at the university hospital, sedation and neuromuscular block were discontinued and the patient became agitated, was thrashing about, moving all four limbs and it was evident that there was increasing surgical emphysema extending down the neck to the lower limbs. On examination, there was no evidence of other injuries. Heart rate was 150 beat min^{-1}, arterial pressure 180/90 mm Hg and heart sounds were normal. Breath sounds were quiet and there was marked surgical emphysema of the neck extending down to the ankles. The results of arterial blood-gas analysis showed pH 7.15, Pa_{CO_2} 10.1 kPa, Pa_{O_2} 46.5 kPa, bicarbonate 26 mmol litre^{-1} and base deficit −3.9 mmol litre^{-1}, with FI_{O_2} 0.5. Abdominal and central nervous system examination revealed no significant findings.

We re-established sedation and neuromuscular block with a combination of morphine, midazolam and vecuronium. There were several episodes where it became difficult to ventilate the lungs manually, but arterial oxygen saturation remained stable. Bronchoscopy was attempted via the tracheal tube but the tracheal lumen could not be identified. A provisional diagnosis of airway discontinuity was made. Chest x-ray at this time showed surgical emphysema and no pneumothorax, while lateral neck x-ray showed evidence of airway discontinuity and no evidence of a cervical spine fracture.

We decided that the patient was too unstable for transport to the operating theatre, because of difficulty in ventilation and increasing subcutaneous air. Ventilation was managed by gentle manual bagging. The patient underwent emergency tracheostomy in the surgical intensive care unit using a size 8 Shiley tracheostomy tube and was taken immediately to the operating room for neck exploration, revision of tracheostomy and tracheal reconstruction. In the operating room, the Shiley tracheostomy tube was replaced with a size 7 armoured tube. The oral tracheal tube inserted at the peripheral hospital was left in place.

Effective gas exchange was maintained using air and oxygen mixtures, and the patient was anaesthetized using a combination of desflurane and morphine, with vecuronium given when necessary to maintain neuromuscular block. The landmarks in the front of the neck were difficult to identify. The patient had complete transection of the trachea between rings one and two. The tracheal tube (fig. 1) was observed to protrude between the first and second tracheal rings. The sternocleidomastoid muscles were transected by the injuries bilaterally. The

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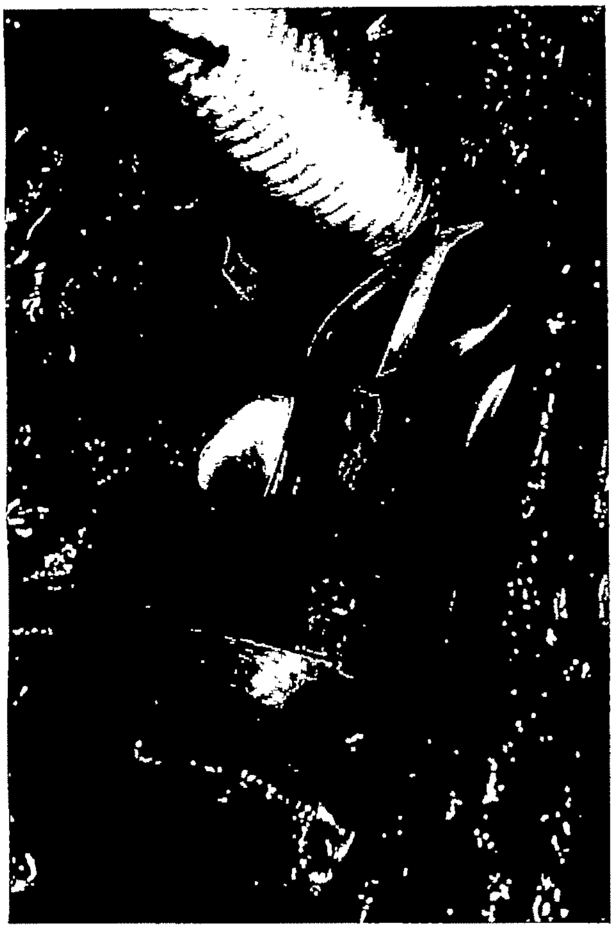

Figure 1 The tracheal tube can be seen protruding through the incompletely disrupted trachea. The armoured tube provided the airway.

internal jugular vein, carotid artery, thyroid cartilage and cricoid cartilages were intact. The trachea was anastomosed and a size 16 Cotton–Lorenz stent was inserted. After closure of the wound, a size 8 Shiley tracheostomy tube was inserted and secured. The immediate postoperative course in the intensive care unit was uneventful and the patient was discharged home after 12 days.

On follow-up, he was managing his tracheostomy well and could talk after plugging the tube. On flexible fibreoptic nasendoscopy, his true vocal cords were in adduction with a small posterior gap of approximately 2 mm.

Discussion

Laryngotracheal trauma is a rare injury, accounting for less than 1% of trauma cases seen in most major centres.[1 2] This rarity is a result of many factors, including rapid death at the scene from asphyxiation,[3] anatomical protection provided by the mandible and sternum,[1] and lack of recognition of minor airway injuries in victims of major trauma by hospital staff.[4]

The extent and location of blunt laryngotracheal trauma is determined by several factors.[5] In one review,[6] 88% of injuries occurred above the fourth tracheal ring. In contrast, penetrating knife and bullet wounds can occur in any part of the cervical trachea. In our case, severe flexion/extension injury resulted in transection between the first and second tracheal rings. Cricoid fracture may result in recurrent laryngeal nerve injury which further compromises the airway lumen.[1 8] In our case, the injury to the recurrent laryngeal nerves was apparent from residual deficit in vocal cord excursion.

The diagnostic signs of laryngotracheal injury include hoarseness, subcutaneous crepitus, dyspnoea, dysphagia, haemoptysis and skin abrasions over the anterior neck,[9] but their presence is variable[5 6 10 11]: surgical emphysema may not develop until hours after the event.[12 13] Increased dyspnoea on extension of the neck is indicative of disruption of the upper airway and was described by Cherry and Hammond.[14] Respiratory distress is often present but even in complete transection, the gap between the ends of the trachea may be sufficiently small to allow ventilation of the lungs to continue.[11]

Definitive investigation and management of a patient with a suspected laryngotracheal injury have been reviewed by Cicala and colleagues,[15] but are dependent on the airway status on arrival at hospital and the presence of associated injuries.[6] Airway control with cervical spine protection is always the priority. Chest and neck x-rays may demonstrate air in subcutaneous tissues or distortion of the laryngotracheal air column. A CT scan has proved beneficial in distinguishing between patients with blunt laryngotracheal trauma who require conservative management and those who require surgical exploration,[16 17] although it is not indicated in patients who obviously require intervention.[18]

Fibreoptic endoscopic examination of the upper airway may help to establish the site and extent of injury: it also enables tracheal intubation while minimizing the risk to the potentially damaged cervical spine.[19] In our patient, a 7.0-mm tracheal tube was passed over a fibreoptic scope. However, this technique can result in airway obstruction[5] and may be technically difficult because of anatomical disruption, bleeding and debris. In our case, the tip of the tube was found to be protruding through the trachea, leading to progression of surgical emphysema with positive pressure ventilation. The Murphy's eye of the tracheal tube, designed to overcome obstruction caused by tracheal wall occlusion, had allowed ventilation of the lungs to occur.

Fitzhugh and Powell recommended tracheostomy as the method of choice to establish an airway in the acutely injured patient with neck trauma,[20] as attempts at tracheal intubation may result in the creation of a false passage, compromising the airway. Rapid deterioration of the patient, as in our case, may also necessitate tracheostomy,[21] which may be performed under local anaesthesia. Alternatively, femoral–femoral cardiopulmonary bypass may be used in an emergency.

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References

1. Gussack GS, Jurkovich GJ, Luterman A. Laryngotracheal trauma: a protocol approach to a rare injury. *Laryngoscope* 1986; **96**: 660–665.
2. Nahum AM. Immediate care of acute blunt laryngeal trauma *Journal of Trauma* 1969; 9: 112–125.

3. Downey WL, Owen RC, Ward PH. Traumatic laryngeal injury—Its management and sequelae. *Southern Medical Journal* 1977; **60**: 756–761.
4. Bryce DP. The surgical management of laryngotracheal injury. *The Journal of Laryngology and Otology* 1972; **86**: 547–587.
5. Sofferman RA. Management of laryngotracheal trauma. *American Journal of Surgery* 1981; **141**: 412–417.
6. Sheely CH II, Mattox KL, Beall AC jr. Management of acute cervical tracheal trauma. *American Journal of Surgery* 1974; **128**: 805–808.
7. Snow JB jr. Diagnosis and therapy for acute laryngeal and tracheal trauma. *Otolaryngologic Clinics of North America* 1984; **17**: 101–107.
8. Lambert GE, McMurray GT. Laryngotracheal trauma: recognition and management. *Journal of the American College of Emergency Physicians* 1976; **5**: 883–887.
9. Alonso WA, Caruso VG, Roncore EA. Minibikes, a new factor in laryngotracheal trauma. *Annals of Otology, Rhinology and Laryngology* 1973; **82**: 800–804.
10. Coetzee T, Van Niekerk JP. Complete subcutaneous rupture—separation of the cervical trachea. *Journal of Trauma* 1965; **5**: 458–463.
11. Urschel HC, Razzuk MA. Management of acute traumatic injuries of tracheobronchial tree. *Surgery, Gynaecology and Obstetrics* 1973; **136**: 113–117.
12. Lusk RP. The evaluation of minor cervical blunt trauma in the pediatric patient. *Clinical Pediatrics* 1986; **25**: 445–447.
13. Soothill EF. Closed traumatic rupture of the cervical trachea. *Thorax* 1960; **15**: 89–92.
14. Cherry JR, Hammond JE. Transection of cervical trachea resulting from closed trauma to the neck. *Journal of Laryngology and Otology* 1984; **98**: 97–100.
15. Cicala RS, Kudsk KA, Butts A, Nguyen H, Fabian TC. Initial evaluation and management of upper airway injuries in trauma patients. *Journal of Clinical Anaesthesia* 1991; **3**: 91–98.
16. Mancuso AA, Hanafee WN. Computed tomography of the injured larynx. *Radiology* 1979; **133**: 139–144.
17. Maceri DR, Mancuso AA, Canalis RF. Value of computed axial tomography in severe laryngeal injury. *Archives of Otolaryngology* 1982; **108**: 449–451.
18. Schaefer SD. Primary management of laryngeal trauma. *Annals of Otology, Rhinology and Laryngology* 1982; **91**: 399–402
19. Roberge RJ, Squyres NS, Demetrpoulos S, McAuliffe M, Vukich D. Tracheal transection following blunt trauma. *Annals of Emergency Medicine* 1988; **17**: 95–100.
20. Fitzhugh GS, Poewll JB. III—Management of laryngotracheal injuries. *Virginia Medical Monthly* 1970; **97**: 490–493.
21. Ayabe H, Tsuji A, Akamine S, Tagawa Y, Kawahara K, Tomita M. Combined transection of the trachea and esophagus following cervical blunt trauma. *Journal of Thoracic and Cardiovascular Surgery* 1993; **41**: 193–195.

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A complication of peribulbar block in a patient with exophthalmos

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Summary

A patient with marked exophthalmos secondary to thyroid eye disease presented for tarsorrhaphy and removal of orbital fat. A single superolateral peribulbar injection was performed. After injection of 3.5 ml of local anaesthetic solution, the globe suddenly dislocated anteriorly. This complication has not been described previously. In patients with exophthalmos, general anaesthesia should be considered as the method of choice for ophthalmic procedures. (*Br. J. Anaesth.* 1998; **81**: 615).

Keywords: surgery, ophthalmological; anaesthetic techniques, regional, peribulbar; complications, exophthalmos

Case report

A 53-yr-old woman with long standing thyroid eye disease presented to the ophthalmic emergency department three times in 12 months complaining of acute, excessive proptosis secondary to coughing. Therefore, it was decided to perform a left tarsorrhaphy and removal of orbital fat. She was euthyroid and apart from being a heavy smoker was otherwise healthy. On examination, she had marked bilateral exophthalmos, which was greater on the left.

The surgeon felt that a single superolateral injection of local anaesthetic would be sufficient for the procedure. After local infiltration to the upper eyelid, a 25-gauge peribulbar needle was inserted periconally to a depth of 2 cm. A slow injection of 2% lidocaine (lignocaine) with epinephrine (adrenaline) and hyaluronidase was commenced. After 3.5 ml had been injected, the entire globe suddenly dislocated anteriorly, with both upper and lower lids lying behind the globe. The block needle was removed promptly and the surgeon exerted gentle but constant pressure manually to the globe which then relocated behind both lids. Local anaesthesia to the upper lid had been achieved and surgery was performed uneventfully.

Discussion

Thyroid eye disease is a common problem, but only a small percentage of patients need surgical intervention.[1] The main indications for surgery are excessive proptosis and optic neuropathy. The aim of surgery is to reduce proptosis and decrease pressure effects on the optic nerve. There have been several surgical procedures described,[2] but the method with least complications is excision of orbital fat.[3 4] In a review of the literature, we found no reports of globe subluxation after peribulbar anaesthesia.

In a normal eye, the globe is prevented from proptosing by the orbital septum. This is a firm, inelastic sheet of connective tissue. It originates superiorly from the periosteum of the superior orbital rim and inserts onto the levator aponeurosis of the upper lid. Similarly, inferiorly it originates from the inferior orbital rim and inserts into the capsulopalpebral fascia (analogous to the upper lid levator aponeurosis) of the lower lid. These attachments retain orbital fat within the orbit and provide anterior stability for the globe.

In thyroid eye disease, intraorbital pressure is increased because of marked thickening of the extrinsic muscles. They may be up to eight times their normal size as a result of an increase in the mucopolysaccharide content of the muscle. The latter has an osmotic effect, leading to the formation of oedema. There is also an increase in orbital fat content, further increasing intraorbital pressure. Fibrosis of the eyelid muscles leads to lid retraction and a further reduction of the stabilizing effect of the orbital septum.

It seems that in this patient, the pressure behind the globe was already increased to a critical level, such that the slight increase in pressure after peribulbar injection was sufficient to cause the globe to sublux anteriorly.

With the increasing use of local anaesthetic techniques we feel that it is important to report this complication. Choice of anaesthetic technique is crucial to the successful outcome of ophthalmic procedures. For patients with marked exophthalmos presenting for orbital decompression, we would suggest that general anaesthesia is the method of choice, thereby avoiding increased pressure behind the globe.

References

1. Kendler DL, Lippa J, Rootman J. The initial clinical characteristics of Graves orbitopathy vary with sex and age. *Archives of Ophthalmology* 1993; 111; 197–201.
2. Garrity JA. The surgical management of Graves ophthalmopathy. *Current Opinion in Ophthalmology* 1994; 5; 39–44
3. Banh RS, Heufelder AE Mechanisms of the disease, Pathogenesis of Graves ophthalmopathy. *New England Journal of Medicine* 1993; 329; 1468–1475.
4. Stark B, Olivari N. Treatment of exophthalmos by orbital fat removal. *Clinics in Plastic Surgery* 1993, 20 285–289.

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Pituitary apoplexy after spinal anaesthesia

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Summary

We report the case of a previously healthy 51-yr-old male who underwent an uneventful total hip replacement under spinal anaesthesia. His immediate postoperative course was complicated by the development of a severe frontal headache. Initial conservative treatment included oral analgesics and an epidural blood patch. The headache persisted and was followed by progressive vision loss and a right partial third nerve palsy. The patient was almost blind at the time of transfer to our neurosurgical unit. Relevant investigations revealed marked hyponatraemia (serum sodium concentration 122 mmol litre^{-1}) and second-degree heart block (Mobitz I). A CT scan showed a pituitary tumour and confirmed the clinical diagnosis of pituitary apoplexy. Urgent craniotomy was scheduled and a large necrotic pituitary adenoma was excised. The postoperative course was uneventful with return of near normal vision at the time of discharge. Clinicians should consider this diagnosis when focal neurological deficits occur with post-dural puncture headache. (*Br. J. Anaesth.* 1998; **81**: 616–618)

Keywords: anaesthetic techniques, subarachnoid; complications, pituitary apoplexy; surgery, craniotomy

Pituitary apoplexy is a rare clinical syndrome resulting from sudden infarction of a normal or adenomatous pituitary gland, which, if left untreated, may result in permanent neurological deficit.[1 2] Symptoms follow rapid enlargement of the gland, compression of the optic chiasma and neighbouring structures, with associated endocrinopathy from pituitary necrosis.

Pituitary apoplexy has been reported after several surgical procedures.[3] Most cases have been associated with cardiopulmonary bypass under general anaesthesia.[4] Our case highlights complications associated with spinal anaesthesia, the clinical presentation of pituitary apoplexy and the potential aetiological factors in this particular patient.

Case report

A 51-yr-old male with osteoarthritis underwent elective total hip replacement in another institution. His past medical history was unremarkable; he received only oral analgesics. His preoperative physical examination was normal and there were no neurological deficits. A spinal anaesthetic technique was used. Intrathecal 0.5% bupivacaine 3 ml was administered via a 25-gauge Whitacre needle in the L3–4 interspace. Systolic arterial pressure decreased from 120 to 90 mm Hg and remained at this level for the duration of the procedure. Estimated intraoperative blood loss was 970 ml. A total of 3000 ml of crystalloid fluid and 1 u. of blood were infused. The immediate postoperative systolic arterial pressure was 90–95 mm Hg.

The patient developed a severe frontal headache 6 h after surgery. Initial conservative management included opioid analgesics. An epidural blood patch was administered 18 h after surgery because of persistence of the headache. Subsequently, the patient began to complain of blurred vision. Twenty-four hours after surgery it was noted that he had developed a partial right third nerve palsy. At this time, he was transferred to our neurosurgical department for further investigation.

On presentation to this institution, the patient had a complete right third nerve palsy, marked ptosis, a fixed dilated pupil and divergent strabismus. Visual acuity was limited to counting fingers on the left and perception of light on the right. He also had a bitemporal visual field defect. Systolic arterial pressure was 95/60 mm Hg and heart rate was 40–60 beat min^{-1}. The electrocardiogram (ECG) showed a Mobitz type I secondary heart block. Haemoglobin concentration was 8.9 g litre^{-1} and he was markedly hyponatraemic (serum sodium concentration 122 mmol litre^{-1}) with normal serum potassium (3.8 mmol litre^{-1})

A clinical diagnosis of pituitary apoplexy was made. Computed tomography (CT) revealed the presence of a pituitary tumour with enlargement of the gland into the cavernous sinus bilaterally, and suprasellar extension compressing the optic chiasma. An urgent right frontotemporal craniotomy and decompression of the pituitary adenoma was undertaken. Hydrocortisone 100 mg was administered i.v. before induction of anaesthesia to treat potential adrenal insufficiency. I.v. fluids and vasopressor support were required during the procedure to maintain systolic arterial pressure at 80–90 mm Hg. The procedure was otherwise uneventful.

Hyponatraemia (sodium 126 mmol litre^{-1}), plasma hypo-osmolarity (262 mmol litre^{-1}), oliguria and urinary hyperosmolarity (645 mmol litre^{-1}) complicated the early postoperative period. Spot urinary sodium was 71 mmol litre^{-1}. Fluid and electrolyte imbalance was treated with supplemental corticosteroids and balanced salt i.v. fluid administration. A diagnosis of panhypopituitarism was confirmed by reduced

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plasma concentrations of thyroid stimulating hormone (TSH) (0. 1 miu litre^{-1}), total tri-iodothyronine (T3) (<0.5 mmol litre^{-1}) and prolactin 17 miu litre^{-1}); serum gonadotrophin concentrations were also low. Visual acuity was virtually normal despite residual partial third nerve palsy and a bitemporal visual field defect on discharge 11 days later.

Discussion

Headache, with an overall incidence of less than 1%, is a well documented complication of spinal anaesthesia since its first introduction by Bier in 1899.[5] Rarely, more serious central neurological sequelae have been reported, including III, IV, VI, and VIIIth cranial nerve palsies. Death resulting from bilateral subdural haematoma has been described after lumbar puncture.[6 7] To the best of our knowledge, there have been no reports of pituitary apoplexy complicating spinal anaesthesia.

Pituitary adenomas represent 10–15% of all intracranial tumours. They are often clinically silent and have been found in up to 20–30% of all subjects in some autopsy series.[8] Although 16.6% of all pituitary tumours removed surgically show histological evidence of infarction, only 6.8% of patients with pituitary adenomas develop the clinical manifestations of pituitary apoplexy. Thus it is a relatively rare complication.[9] Most cases occur spontaneously and it is frequently the first manifestation of a pituitary adenoma, as occurred in our patient.

There were no abnormal neurological features in our patient before operation. The frontal headache that developed after operation was initially treated conservatively with routine analgesics. However, the patient failed to improve and in the absence of other neurological deficits at this time, a diagnosis of post-dural puncture headache was made. Epidural blood patch has been reported to produce almost immediate relief in up to 89% of post-dural puncture headaches.[10 11] With the onset of visual symptoms, other diagnoses considered included subarachnoid aneurysm haemorrhage, meningitis, pituitary apoplexy, midbrain infarction, encephalitis, cavernous sinus thrombosis, carotid artery aneurysm and parasellar tumour. A CT scan was the initial investigation and confirmed the presence of a large pituitary tumour with lateral extension into the cavernous sinus and suprasellar compression of the optic chiasma.

Pituitary apoplexy may follow sudden infarction or haemorrhage into the gland, which causes it to swell and compress adjacent structures. The clinical presentation of this patient was typical of fulminant pituitary apoplexy. The symptoms arise as a result of three processes: (1) leakage of blood or necrotic tissue into the subarachnoid space may be associated with headache, neck stiffness and photophobia; (2) pressure effects—superior extension of the pituitary gland may compress the optic chiasma resulting in loss of visual acuity and visual field defects. Hypothalamic dysfunction may be associated with alterations in temperature, respiration and cardiac function. This hypothalamic dysfunction may account for the transient Mobitz I secondary degree heart block noted in this case. Lateral extension of the gland may cause ocular palsies in up to 40% of cases as a result of compression of III, IV and VIth cranial nerves in the cavernous sinus[2 12]; (3) endocrinopathy—acute adrenal insufficiency, observed in up to 66% of such cases, is the most important endocrine dysfunction after pituitary apoplexy.[13] Intraoperative hypotension and hyponatraemia persisting into the postoperative period may have been manifestations of acute adrenal insufficiency in this case. Glucocorticoids are necessary for maintenance of pressor tone and glomerular filtration. Glucocorticoid insufficiency affects the ability of the renal tubules to excrete water. In addition, normal values for serum potassium were consistent with acute secondary adrenal insufficiency. Mineralocorticoid function may be unaffected because the renin–angiotensin–aldosterone axis is relatively independent of the ACTH–adrenal axis.[14] The syndrome of inappropriate anti-diuretic hormone secretion was considered as an alternative cause but this has been reported rarely in association with pituitary apoplexy.[15]

Aetiological factors in the pathogenesis of pituitary apoplexy are not well understood. Elevated oestrogen states, bromocriptine therapy, irradiation and diabetes have been implicated,[15–17] but the majority occur spontaneously without identifiable precipitating factors.[1 15] It has been suggested that the adenomatous gland may "outstrip" its own blood supply at a variable critical time and produce ischaemic necrosis followed by haemorrhage into the gland.[15]

Intraoperative hypotension could be considered as an aetiological factor in our patient because systolic arterial pressure was reduced from 120 to 90 mm Hg after administration of spinal anaesthesia. There is some evidence to suggest that pituitary tumours may be particularly susceptible to changes in systemic arterial pressure. Bevan and colleagues[18] described a case of pituitary apoplexy after administration of oral isosorbide mononitrate in which a patient developed severe headache within 90 min of ingesting the drug. A month later, severe headache, this time associated with persistent neurological deficits, followed attempts to restart drug administration. The patient was subsequently diagnosed as having pituitary apoplexy. The association of the vasodilator properties of the drug and the onset of apoplexy seemed likely.

Lever and colleagues[19] reported on the onset of apoplexy after a thyrotrophin releasing factor (TRF) stimulation test and Bernstein, Hegele and Gentili[20] also reported a case of apoplexy after a "triple bolus" test (a pituitary stimulation test using TRH, LHRH and insulin). Both attributed significance to the norepinephrine (noradrenaline) releasing properties of TRH which may induce vasospasm precipitating pituitary infarction.

The pituitary gland is supplied by end arteries which are poorly innervated and operate at a low hydrostatic pressure.[21] The vessels within the tumour itself are abnormal. They are typically smaller, variable in number, poorly fenestrated and have irregular, ruptured basement membranes. In addition, the expanding mass may directly compress the infundibulum or the superior hypophyseal artery and impair blood supply to the entire anterior lobe. As a result of these anatomical features, an adenomatous pituitary is susceptible to infarction with relatively minor changes in perfusion pressure.[1] Low perfusion pressure was the suggested cause of apoplexy in the cases associated with cardiopulmonary bypass.[4] Other considerations included embolization of platelet aggregates, atherosclerotic plaques or gas bubbles, and anticoagulation with inadequate reversal. Pituitary tumours are known to be susceptible to haemorrhage, observed in approximately 17% of adenomas.[15] This is a variable finding in apoplexy and was not present in our patient.

Another, although perhaps less likely, mechanism of pituitary apoplexy was a reduction in CSF pressure secondary to CSF leak. Minor alterations in pressure gradients within the skull have been associated with the onset of apoplexy.[1] These include lumbar puncture for pneumoencephalography, repetitive coughing and sneezing secondary to upper respiratory tract infections, minor head trauma, mechanical ventilation and scuba diving.

In summary, we believe this is the first case report of pituitary apoplexy complicating spinal anaesthesia. Pituitary adenomas are frequently asymptomatic and are thus difficult to diagnose before operation. However, this case highlights the importance of prompt assessment of patients with post-dural puncture headache and clinicians should consider the diagnosis of pituitary apoplexy when focal neurological deficits are also present.

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References

1. Cardoso E, Peterson E. Pituitary apoplexy, a review. *Neurosurgery* 1984; 14: 363–373.
2. McFadzean R, Doyle D, Rampling R, Teasdale E. Pituitary apoplexy and its effect on vision. *Neurosurgery* 1991; **29**: 669–675.
3. Yahagi A, Nishikawa S, Matsui Y, Komoda Y, Amakata Y. Pituitary apoplexy following cholecystectomy. *Anaesthesia* 1992; 47: 234–236.
4. Shapiro L. Pituitary apoplexy following coronary artery bypass surgery. *Journal of Surgical Oncology* 1990; 44: 66–68.
5. Mihic D. Post spinal headache and relationship of the needle to longitudinal dural fibres. *Regional Anaesthesia* 1985; **10**: 76–79.
6. Vandam L, Dripps R. Long term follow up of patients who received 10,098 spinal anaesthetics. Syndrome of decreased intracranial pressure (headache and occular and auditory difficulties). *Journal of the American Medical Association* 1956; **161**: 586–591.
7. Endleman J, Wingard D. Subdural hematomas after lumbar puncture. *Anesthesiology* 1980; **52**: 166–168.
8. Annegers JF, Coulan CB, Laws ER. Pituitary tumors: Epidemiology. In: Givens JR, ed. *Hormone-Secreting Pituitary Tumors*. Chicago: Year Book Medical Publishing 1982; 393.
9. Wakai S, Fukushima T, Teramoto A, Sano K. Pituitary apoplexy: its incidence and clinical significance. *Journal of Neurosurgery* 1981; **55**: 187–193.
10. Gormley J. Treatment of post spinal headache. *Anesthesiology* 1960; **21**: 565–566.
11. DiGiovanni A, Dunbar B. Epidural injections of autologous blood for post lumbar puncture headache. *Anesthesia and Analgesia* 1970; **49**: 226–232.
12. Rolich C, Ober P. Pituitary apoplexy. *Endocrinology and Metabolism Clinics of North America* 1993; **22**: 291–302.
13. Veldhuis J, Hammond J. Endocrine function after spontaneous infarction of the human pituitary: Report, review, and reappraisal. *Endocrine Reviews* 1980; **1**: 100–107.
14. Gaillard RC. Pituitary gland emergencies. *Baillière's Clinical Endocrinology and Metabolism* 1992; **6**: 57–75.
15. Reid R, Quigley M, Yen S. Pituitary apoplexy, a review. *Archives of Neurology* 1985; **42**: 712–719.
16. Nagulesparan M, Roper J. Haemorrhage into the anterior pituitary during pregnancy after induction of ovulation with clomiphene. A case report. *British Journal of Obstetrics and Gynaecology* 1978; **85**: 153–155
17. Uilhein A, Balfour W, Donovan P. Acute haemorrhage pituitary adenomas. *Journal of Neurosurgery* 1957; **14**: 140–151.
18. Bevan J, Oza A, Burke C, Adams C. Pituitary apoplexy following isosorbide administration. *Journal of Neurology, Neurosurgery and Psychiatry* 1987; **8**: 104–105.
19. Lever E, Butler J, Cox R, McCabe J. Infarction of growth hormone producing pituitary macroadenoma by TRH. *Journal of Endocrinology* 1985; **104** (Suppl. 87).
20. Bernstein M, Hegele R, Gentili F. Pituitary apoplexy associated with a triple test. *Journal of Neurosurgery* 1984; **61**: 586–590.
21. Flerko B. The hypophyseal portal circulation today. *Neuroendocrinology* 1980; **30**: 56–63.

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Epidural anaesthesia for Caesarean section in an achondroplastic dwarf

M. J. MORROW AND I. H. BLACK

Summary

We describe the anaesthetic management of a parturient with achondroplasia presenting for Caesarean section under epidural anaesthesia. A block extending from T4 to S4 was established over 25 min using a total of 12 ml of 2.0% lidocaine (lignocaine) with epinephrine (adrenaline) 1:200 000 and fentanyl 37.5 μg. Apart from mild discomfort during peritoneal incision, her perioperative course was uneventful. Achondroplasia is reviewed and the anaesthetic implications of the condition are discussed. (*Br. J. Anaesth.* 1998; **81**: 619–621).

Keywords: anaesthesia, obstetric; anaesthetic techniques, epidural; genetic factors; complications, achondroplasia

Dwarfism is defined as failure to achieve a height of 148 cm by adulthood.[1] More than 100 different types of dwarfism have been described, but the commonest form of this relatively rare condition is achondroplastic dwarfism.[2] The characteristic spinal and craniofacial abnormalities of achondroplasia occur as a consequence of normal periosteal bone deposition coupled with failure of endochondral bone formation. The usual appearance includes a large head, saddle nose, short limbs and a relatively normally proportioned trunk, often associated with marked kyphoscoliosis and lumbar lordosis. Limited neck extension, foramen magnum stenosis, a large tongue, large mandible and atlanto-axial instability are commonly encountered, making general anaesthesia potentially hazardous.

An exaggerated lumbar lordosis, thoracic kyphoscoliosis, generalized spinal stenosis and the unpredictable behaviour of local anaesthetic drugs in the epidural and subarachnoid spaces have, however, led to a reluctance among anaesthetists to consider regional anaesthesia in this group of patients. When combined with the well documented anaesthetic risks encountered during the third trimester of pregnancy of acid aspiration, decreased cardiorespiratory reserve and supine hypotension, the management of the gravid achondroplastic dwarf for Caesarean section presents a significant challenge for the anaesthetist, whether general or regional anaesthesia is chosen.

Case report

A 28-yr-old primagravid achondroplastic dwarf presented for elective Caesarean section at 37 weeks' gestation. Her only previous general anaesthetic (as a child for tonsillectomy) had apparently been uneventful, but no notes relating to this procedure were available. Her pregnancy had been uneventful and ultrasonic measurements *in utero* suggested that the fetus was normally developed.

Physical examination revealed a 64-kg, 120-cm healthy female with the typical features of achondroplasia: large head, short limbs and marked kyphoscoliosis of the thoracolumbar spine. She had a short neck, large tongue and full set of teeth; the lower lumbar vertebrae were impalpable. Neck extension was limited and it was possible to see only the uvula when the tongue was fully protruded. Examination of the cardiorespiratory system revealed no problems and there were no neurological abnormalities. Preoperative haemoglobin and electrolyte concentrations were within normal limits.

The patient expressed a desire to be awake for birth. Therefore, after discussion of the potential risks and benefits of general compared with regional anaesthesia for Caesarean section, it was decided to perform the operation under epidural anaesthesia. The patient was made aware that a general anaesthetic may be required in the event of failed epidural block.

Premedication comprised ranitidine 150 mg orally on the evening before surgery and again on the morning of the operation. On arrival in the operating room, 30 ml of sodium citrate 0.3 mol litre^{-1} was administered orally, and invasive radial arterial pressure monitoring established under local anaesthesia. Other monitoring included ECG and pulse oximetry. A 16-gauge i.v. cannula was inserted and 750 ml of compound sodium lactate solution was administered before siting the epidural catheter. Facilities for emergency and fibreoptic intubation were available.

The patient was placed in the sitting position and the epidural space located at the L3–4 interspace using a 16-gauge Tuohy needle and the loss of resistance to saline technique. The needle was inserted at an angle of approximately 40° to the skin in a cephalad direction and directed towards the predicted midline. The epidural space was located with minimal difficulty at a depth of 4.5 cm, and 2.5 cm of catheter were threaded. A continuous flow of blood was obtained on aspiration of the catheter and therefore it was withdrawn. The procedure was repeated in the same interspace but with the needle realigned slightly further towards the anticipated midline. Again the space was located at 4.5 cm, and 2.0 cm of catheter were advanced, this time uneventfully. With the patient remaining in the sitting position, a test dose of 1.5 ml of 2% lidocaine (lignocaine) with

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epinephrine (adrenaline) 1:200 000 was administered without evidence of a subarachnoid block developing after 5 min. Another 6 ml of the same solution was administered in the sitting position in two increments at 5-min intervals. The patient was then placed in the right lateral position and another 3 ml of solution administered. This was followed 5 min later by another 3 ml in the left lateral position. At this stage fentanyl 37.5 μg was administered via the epidural catheter. The patient was then placed in the modified supine position with 15° of left lateral tilt and the extent of the block assessed. After 25 min a sensory block to temperature and fine touch extended from S4 to T4 on the left side and from S4 to T3 on the right. A total of 15 mg of ephedrine i.v. were administered during establishment of the epidural block in response to an anticipated decrease in arterial pressure.

Caesarean section was performed using a midline incision and good muscle relaxation was observed throughout the procedure. The patient experienced a brief episode of discomfort during peritoneal traction which was relieved rapidly by administration of a 50:50 mixture of nitrous oxide in oxygen. A healthy male infant weighing 3545 g was delivered with an Apgar score of 8 at 1 min and 9 at 5 min. No features of achondroplasia were evident. Syntocinon 10 u. i.v. were administered after cord clamping and a further 20 u. added to an i.v. infusion of compound sodium lactate solution 1000 ml.

Maternal heart rate and arterial pressure were well maintained throughout the procedure. Blood loss at the end of operation was estimated at 300 ml. The patient's partner was present throughout. On completion of the procedure the patient was transferred to the high dependency area, where monitoring was continued until the block had worn off. Analgesia was provided by a suppository of diclofenac 100 mg inserted at the end of the procedure and a patient-controlled analgesia system set to deliver morphine 1-mg boluses at 5-min intervals. Full recovery of neuromuscular function had occurred within 8 h and no complications were reported. Mother and baby were discharged from hospital on day 7 without further incident.

Discussion

Achondroplasia is the commonest form of dwarfism, with an incidence of 0.5–1.5 per 10 000 live births.[2 3] The condition is transmitted in an autosomal dominant fashion, but only 20% of cases are familial, the remaining 80% representing a spontaneous genetic mutation.[4] Females are affected more frequently than males.[5] Achondroplastic dwarfs characteristically have low fertility rates[4]; however, those that do conceive often require delivery by Caesarean section because the normal-sized fetal head and smaller than normal maternal pelvic diameter results in cephalopelvic disproportion during the later stages of pregnancy.

Anaesthesia, whether general or regional, presents many potential problems during the latter stages of pregnancy. Maintenance of a patent upper airway may be difficult because of the presence of a large tongue and large mandible, usually associated with a full set of teeth.[6] Tracheal intubation may prove difficult as foramen magnum stenosis and cervical spine instability are common, and hyperextension of the neck must be avoided to prevent cervical cord compression.[6–9] Limited neck extension has been reported as a cause of difficult intubation in two cases,[7 8] although not all authors have encountered similar difficulties. Mayhew and colleagues[6] reported no difficulty in airway management or direct laryngoscopy in a series of 27 patients undergoing 36 anaesthetic procedures. If tracheal intubation is required in this group of patients, a small tracheal tube should be selected, the most appropriate size being predicted according to weight rather than age.[6]

Cardiorespiratory function may be impaired by several factors specific to achondroplasia and other less common forms of dwarfism. Thoracic kyphoscoliosis, upper airway obstruction, rib deformities and recurrent respiratory tract infections are common.[2 10] Failure of the normal-sized fetal head to engage in the narrow pelvic inlet results in the uterus remaining an entirely intra-abdominal organ during the latter stages of pregnancy. The subsequent diaphragmatic splinting causes a greater than usual pregnancy-induced reduction in functional residual capacity.[11] By the 16th week, these patients appear to be in the 30th week of pregnancy.[1] Cor pulmonale is a relatively rare occurrence but has been reported as a consequence of these multiple respiratory complications.[2 10 12]

Epidural anaesthesia may be technically difficult to perform because of the significant anatomical abnormalities often associated with achondroplasia. Marked lumbar lordosis and thoracic kyphoscoliosis may make identification of bony landmarks difficult. Reduced interpedicular distance, shortened pedicles, osteophyte formation[13] and prolapsed intervertebral discs combined with a narrow epidural space may make identification of the space difficult and increase the risk of dural puncture.[2] The presence of a narrow epidural space may also, as in this case, make insertion of the catheter difficult.[2] Engorged epidural veins increase the risk of venous puncture either by the Tuohy needle or the catheter, and result in an unpredictable spread of local anaesthetic within the space.[14] Spinal stenosis may impair free flow of CSF and make identification of dural puncture more difficult.[14] Aorto-caval compression may be particularly severe during regional anaesthesia as a result of the intra-abdominal position of the uterus.[4 11 14] Left uterine displacement, vigorous fluid preloading and vasopressor support have been advocated.[15]

It has been suggested that regional anaesthesia should be avoided in patients with achondroplasia because any subsequent neurological abnormalities caused by spinal deformities might be attributed to the anaesthetic technique.[7] But no neurological complications in patients with achondroplasia have yet been reported in those cases performed under regional anaesthesia. As there were no pre-existing neurological problems in our patient, it was felt that there were no specific contraindications to the use of epidural anaesthesia. In common with previous experiences, no neurological sequelae developed.

There are no guidelines on the use of epidural or spinal local anaesthetics in the gravid achondroplastic dwarf. Because of the large inter-individual variation in spinal column anatomy in these patients, it is unlikely that clear recommendations could be developed. What is clear, however, is that great care must be taken when establishing regional block in these situations, regardless of the local anaesthetic chosen or the technique used.

The most appropriate type and volume of epidural test dose is unclear. Plain 0.5% bupivacaine in doses of 2.0 ml[4] and 3.0 ml[14] have been reported while 1.0 ml of carbonated lidocaine with epinephrine 1:200 000 has also been described.[16] Crawford and Dutton[17] reported the use of a 32-gauge microspinal catheter to allow the establishment of continuous spinal anaesthesia in an achondroplastic dwarf, but these catheters have been withdrawn because of concerns about the incidence of neurological deficits associated with their use. Infusion of 0.5 ml of 0.5% hyperbaric plain bupivacaine intrathecally resulted in a bilateral block to T6 associated with significant hypotension developing within 20 min. Therefore, it would seem prudent to reduce the volume of the test dose in this group of patients; consequently, we chose to use 1.5 ml of lidocaine with epinephrine 1:200 000.

The volume of solution needed to produce surgical block is also unclear. Brimacombe and Caunt[4] reported the development of an epidural block extending from C5 to S4 over a 20-min period using 0.5% plain bupivacaine 12 ml, while Wardall and Frame[14] reported that only 5 ml of 0.5% plain bupivacaine was sufficient to develop a block to T4. Cohen[11] reported adequate block with a total of 9 ml of 3% 2-chloroprocaine, supplemented with another 9 ml after 35 min. Carstoniu, Yee and Halpern[16] achieved adequate block for Caesarean section using 8 ml of 2.0% carbonated lidocaine with epinephrine 1:200 000. The use of epidural fentanyl to supplement surgical block in this group of patients has not been reported previously.

Anaesthesia poses a significant risk to patients with achondroplasia and this must be recognized by all staff involved in the perioperative care of these patients. Early communication with the anaesthetic team is important and a thorough preoperative assessment is mandatory. Facilities for managing the difficult airway and suitably experienced personnel should be available and the use of intra-arterial pressure monitoring should be considered in patients with co-existing cardiorespiratory problems. If opioid supplementation of the block is used, frequent monitoring of vital signs and continuous pulse oximetry should be considered during the postoperative period. If these factors are borne in mind and the procedure is undertaken with adequate expertise and support facilities then the use of epidural anaesthesia is a satisfactory technique for Caesarean section in the gravid achondroplastic dwarf.

References

1. Tyson JE, Barnes AC, McKusick VA, Scott CI, Jones GS Obstetric and gynecologic considerations of dwarfism. *American Journal of Obstetrics and Gynecology* 1970; **108**: 688–703.
2. Berkowitz ID, Raja SN, Bender KS, Kopits SE Dwarfs. Pathophysiology and anesthetic implications. *Anesthesiology* 1990; 73: 739.
3. Orioli IM, Castilla EE, Barbosa-Neto JG. The birth prevalence rates for the skeletal dysplasias. *Journal of Medical Genetics* 1986, **23**: 328.
4. Brimacombe JR, Caunt JA. Anaesthesia in a gravid achondroplastic dwarf. *Anaesthesia* 1990; **45**: 132–134
5. Murdoch JL, Walker BA, Hall JG, Abbey H, Smith KK, McKusick VA. Achondroplasia—a genetic and statistical survey. *Annals of Human Genetics* 1970; **33**: 227–244.
6. Mayhew JF, Katz J, Miner M, Leiman BC, Hall ID Anaesthesia for the achondroplastic dwarf *Canadian Anaesthetists Society Journal* 1986; **33**: 216
7. Walts LF, Finerman G, Wyatt GM. Anaesthesia for dwarfs and other patients of pathological small stature. *Canadian Anaesthetists Society Journal* 1975; **22**: 703
8. Mather JS. Impossible direct laryngoscopy in achondroplasia. *Anaesthesia* 1966; **21**: 244–248.
9. Kalla GN, Fening E, Obiaya MO. Anaesthetic management of achondroplasia. *British Journal of Anaesthesia* 1986; **58**: 117–119.
10. Stokes DC, Phillips JA, Leonard CO, Dorst JP, Kopits SE, Trojak JE, Brown DL. Respiratory complications of achondroplasia *Journal of Pediatrics* 1983; **102**: 534.
11. Cohen SE. Anesthesia for Cesarean section in achondroplastic dwarfs. *Anesthesiology* 1980; **52**: 264–266.
12. Levin DL, Muster AJ, Pachman LM, Wessel HU, Paul MH, Koshaba J. Cor pulmonale secondary to upper airway obstruction. Cardiac catheterization, immunologic and psychometric evaluation in nine patients. *Chest* 1975, **68**: 166–171.
13. Wynne-Davies R, Walsh WK, Gormley J Achondroplasia and hypochondroplasia. Clinical variation and spinal stenosis. *Journal of Bone and Joint Surgery* 1981; **63**: 508–515
14. Wardall GJ, Frame WT. Extradural anaesthesia for Caesarean section in achondroplasia. *British Journal of Anaesthesia* 1990, **64**: 367–370
15. Ratner EF. Cohen SE. Parturients of short stature. In Gambling DR, Douglas MJ, eds. *Obstetric Anaesthesia and Uncommon Disorders.* Philadelphia: WB Saunders, 1998, 183–194.
16. Carstoniu J, Yee I, Halpern S. Epidural anaesthesia for caesarean section in an achondroplastic dwarf. *Canadian Journal of Anaesthesia* 1992; **39**: 708.
17. Crawford M, Dutton DA. Spinal anaesthesia for caesarean section in an achondroplastic dwarf. *Anaesthesia* 1992, 47. 1007.

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Transient radicular irritation after spinal anaesthesia with 2% isobaric mepivacaine

S. SIA AND C. PULLANO

Summary

Several cases have been reported in which symptoms suggestive of transient radicular irritation occurred after the use of lidocaine (lignocaine) for spinal anaesthesia. We report three patients in whom we observed similar symptoms after uneventful spinal anaesthesia using isobaric 2% mepivacaine. (*Br. J. Anaesth.* 1998; **81**: 622–624).

Keywords: anaesthetic techniques, subarachnoid; anaesthetics local, mepivacaine; complications, transient radicular irritation

In 1993, Schneider and colleagues published four case reports of transient neurological toxicity after uneventful single-injection spinal anaesthesia with 5% hyperbaric lidocaine (lignocaine).[1] The term transient radicular irritation (TRI) has been used to describe the syndrome. A common feature of all of these cases was moderate to severe pain in the buttocks, lower back and/or legs, appearing after complete recovery from spinal anaesthesia. Since then, 5% hyperbaric, 2% hyperbaric and 2% isobaric solutions of lidocaine have been implicated in TRI.[2–6] More recently, several reports have suggested that TRI is not restricted to the use of lidocaine.[7–9] We report three possible cases of TRI occurring after subarachnoid administration of 2% isobaric mepivacaine in patients undergoing surgery in the lithotomy position.

Case reports

PATIENT NO. 1

A 56-yr-old, 158-cm, 60-kg woman was undergoing diagnostic hysteroscopy and curettage for irregular uterine bleeding. She has undergone two uneventful general anaesthetics, 7 and 3 yr earlier, for minor surgical procedures. There was no history of chronic back pain, diabetes or neurological disturbances. Physical examination and routine preoperative tests, including coagulation studies, were normal. With the patient in the sitting position, skin preparation was performed with an iodine-containing solution. After removing excess moisture from the disinfected site, subarachnoid puncture was performed at the first attempt without difficulty at the L3–4 interspace using a 25-gauge Whitacre needle. After aspiration of clear cerebrospinal fluid, 2% plain mepivacaine 3 ml was given over 10 s. No paraesthesia was elicited during insertion of the needle or administration of the anaesthetic. The patient was turned on her back and, after 10 min, placed in the lithotomy position. Sensory block to pinprick was obtained at T8.

The surgical procedure was uneventful and lasted 40 min. Haemodynamic values remained stable during the intraoperative period. The immediate postoperative period was uneventful, with full recovery from spinal anaesthesia. Six hours after operation the patient developed bilateral burning pain in the buttocks radiating to the dorsolateral sides of both thighs and calves. Neurological examination revealed no sensory–motor or muscle–tendon reflex abnormalities and she was able to walk. Lasègue's test was negative. Sphincter tone was normal. She had no headache, tinnitus or diplopia. Analgesic therapy with ketorolac tromethamine reduced the symptoms and the patient was discharged on the evening of the first day after operation. At a telephone interview 3 days later, the patient reported complete resolution of the pain sensation.

PATIENT NO. 2

A 69-yr-old, 177-cm, 65-kg man presented for endoscopic removal of vesical papillomata. The patient's medical history included hypertension and COPD. There was no history of chronic back pain, peripheral neuropathy or diabetes. Physical examination and preoperative results of coagulation studies were normal. Nine months earlier he had undergone transurethral resection of the prostate (TURP) under uneventful spinal anaesthesia using 0.5% plain bupivacaine 3 ml via a 25-gauge Quinke needle. With the patient in the sitting position and using the same procedure as described in patient No. 1, dural puncture was performed without difficulty at the L3–4 interspace using a 25-gauge Quinke needle. Injection of 2% plain mepivacaine 3 ml was performed over 10 s. There was no paraesthesia, pain or bleeding during placement of the needle or injection of local anaesthetic. The patient was turned on his back and placed in the lithotomy position. An upper level of anaesthesia of T9 was obtained after 15 min. The surgical procedure, lasting 45 min, was uneventful as was the postoperative recovery. The patient remained haemodynamically stable during the procedure.

Ten hours after operation, he developed bilateral pain radiating from the lower part of the back to the

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calves. Neurological examination by a consultant neurologist revealed no sensory–motor or muscle–tendon abnormalities. Lasègue's test was negative. He had no headache, tinnitus, diplopia or signs of bowel dysfunction. Mefenamic acid provided pain relief. His urinary catheter was removed 2 days after operation and he voided successfully. The patient was discharged 3 days after operation with complete resolution of symptoms.

PATIENT NO. 3

A 42-yr-old, 165-cm, 53-kg woman was undergoing diagnostic hysteroscopy and curettage. Her medical history was uneventful. Physical examination and laboratory studies were unremarkable. With the patient in the right lateral decubitus position and using a sterile technique as in patient No. 1, a 27-gauge Whitacre needle was introduced into the subarachnoid space at the first attempt at the L3–4 interspace. Injection of 2% isobaric mepivacaine 3 ml was given over 10–15 s. No discomfort was elicited during insertion of the needle or during injection of local anaesthetic. An upper sensory level of T8 was obtained. The gynaecological procedure, lasting 35 min, and performed in the lithotomy position, was uneventful. Haemodynamic values remained stable throughout the intraoperative period.

Seven hours after operation, after complete recovery from anaesthesia, severe burning pain developed in the buttocks radiating to the dorsolateral sides of both thighs and calves. Analgesic therapy with mefenamic acid did not relieve the symptoms and the patient was given morphine 10 mg i.m. Neurological examination by a consultant neurologist on the first day after operation revealed no sensory disturbances, change in muscle strength or difficulties in voiding. Lasègue's test was negative. The patient was discharged 2 days after operation. During a telephone interview 5 days later, the patient reported no pain but she pointed out that she would refuse to have spinal anaesthesia in future.

Discussion

Spinal anaesthesia is used at our institution for patients undergoing surgical procedures on the lower abdomen and legs, provided that they give consent. Lidocaine is our primary choice for short surgical procedures. After several cases of TRI associated with subarachnoid administration of 2% lidocaine, we considered it appropriate to try an alternative drug for short-term surgery. We chose 2% mepivacaine because it was the only local anaesthetic available at our institution which has a similar duration of action to 2% lidocaine.[10]

There are many potential causes for postoperative neurological sequelae after spinal anaesthesia. In our patients, it is unlikely that TRI was caused by direct trauma to neural tissue, as there was no bleeding and no paraesthesia associated with the anaesthetic. Ischaemia of the spinal cord can be disregarded as an important co-factor because arterial pressure was stable in all patients. Infection or chemical contamination of cerebrospinal fluid seems unlikely as a strict aseptic technique was used. Chronic lumbar disc pathology was also probably unlikely as patients had no history of chronic back pain.

The clinical courses of our patients were remarkably similar to those of previous cases of TRI after intrathecal administration of lidocaine[1–6] and suggest that a direct effect of the anaesthetic solution at the sacral nerve roots is more likely. Few studies have evaluated the incidence of TRI after mepivacaine spinal anaesthesia. Hiller and Rosemberg reported an incidence of 30% in patients who received 4% spinal hyperbaric mepivacaine compared with 3% in those who had received 0.5% hyperbaric bupivacaine.[7] The authors thought that decreasing the dose of mepivacaine may diminish the development of TRI. Our cases indicate that decreasing the concentration and dose of mepivacaine does not prevent development of TRI.

However, in addition to a toxic effect of local anaesthetic, another possible co-factor in the development of TRI should be taken into account. All of our patients underwent surgery in the lithotomy position. Recent literature has focused on the importance of surgical position in the incidence of TRI,[2–5 7 9 11] as most cases were performed in the lithotomy position.[1–4 6 9 11 12] Patient positioning *per se* seemed an unlikely cause of our patients' symptoms, as duration of surgery was very short. Nevertheless, the lithotomy position may contribute to transient neurological symptoms by stretching the cauda equina and sciatic nerves, thus decreasing the vascular supply and increasing vulnerability to injury.[1] Pollock and colleagues showed that there was a significant difference in the incidence of TRI between patients undergoing surgery in the lithotomy position and those in the supine position.[13] Freedman and colleagues, in a multicentre study, reported an incidence of TRI after lidocaine administration of 2.9% in patients undergoing surgery in the supine position compared with 21.8% in the lithotomy position.[14] Thus we cannot exclude the possibility that isobaric mepivacaine can be used safely in a lower risk population, that is in patients not in the lithotomy position. In support of this, Zayas, Liguori and Chisholm, in patients undergoing knee arthroscopy, reported no case of TRI in patients receiving 1.5% mepivacaine 45 mg compared with an incidence of 22% in those receiving 2% lidocaine 60 mg.[15]

Mepivacaine was used for spinal anaesthesia in our institution during the 4-month period from 1 March to 30 June 1997. During this period 56 patients received 2% mepivacaine for short-term surgery. Of these, 33 patients underwent surgery in the supine position, 23 for knee arthroscopy and 10 for inguinal hernia repair. The remaining 23 patients were positioned in the lithotomy position, 12 for minor gynaecological procedures and 11 for transurethral surgery. We did not observe any case of TRI in patients undergoing surgery in the supine position. During the same period no cases of TRI were noted in the 172 patients receiving bupivacaine for spinal anaesthesia. However, as this was not a prospective survey, failure to detect TRI may reflect inadequate patient assessment.

In summary, our cases indicate that TRI may occur after the use of an isobaric solution of 2% mepivacaine. Prospective randomized studies are warranted to evaluate the incidence of this syndrome after administration of spinal mepivacaine and the potential interaction between local anaesthetics and surgical positioning.

References

1. Schneider M, Ettlin T, Kaufmann M, Schumaker P, Urwyler A, Hampl K, von Hochstetter A. Transient neurologic toxicity after hyperbaric subarachnoid anesthesia with 5% lidocaine. *Anesthesia and Analgesia* 1993; **76:** 1154–1157.
2. Salmela L, Aromaa U, Cozanitis DA. Leg and back pain after spinal anaesthesia involving hyperbaric 5% lignocaine. *Anaesthesia* 1996; **51:** 391–393.
3. Hampl KF, Schneider MC, Bont A, Pargger H. Transient radicular irritation after single subarachnoid injection of isobaric 2% lignocaine for spinal anaesthesia. *Anaesthesia* 1996; **51:** 178–181.
4. Hampl KF, Schneider MC, Pargger H, Gut J, Drewe J, Drasner K. A similar incidence of transient neurological symptoms after spinal anesthesia with 2% and 5% lidocaine. *Anesthesia and Analgesia* 1996; **83:** 1051–1054.
5. Pollock JE, Neal JM, Stephenson CA, Wiley CE. Prospective study of the incidence of transient radicular irritation in patients undergoing spinal anesthesia. *Anesthesiology* 1996; **84:** 1361–1367.
6. Ramasamy D, Eadie R. Transient radicular irritation after spinal anaesthesia with 2% isobaric lignocaine. *British Journal of Anaesthesia* 1997; **79:** 394–395.
7. Hiller A, Rosemberg PH. Transient neurological symptoms after spinal anaesthesia with 4% mepivacaine and 0.5% bupivacaine. *British Journal of Anaesthesia* 1997; **79:** 301–305.
8. Sumi M, Sakura S, Kosaka Y. Intrathecal hyperbaric 0.5% tetracaine as a possible cause of transient neurologic toxicity. *Anesthesia and Analgesia* 1996; **82:** 1076–1077.
9. Tarkkila P, Huhtala J, Tuominen M, Lindgren L. Transient radicular irritation after bupivacaine spinal anesthesia. *Regional Anesthesia* 1996; **21:** 26–29.
10. Strichartz GR, Berde CB. Local anesthetics. In: Miller RD, ed. *Anesthesia*, 4th Edn. New York: Churchill Livingstone, 1994; 489–521.
11. Sjöstrom S, Bläss J. Severe pain in both legs after spinal anaesthesia with hyperbaric 5% lignocaine solution. *Anaesthesia* 1994; **49:** 700–702.
12. Hampl KF, Schneider MC, Ummenhofer W, Drewe J. Transient neurologic symptoms after spinal anesthesia. *Anesthesia and Analgesia* 1995; **81:** 1148–1153.
13. Pollock JE, Neal JM, Stephenson CA, Wiley CE. The importance of surgical positioning and anesthetic concentration in the incidence of transient radicular irritation. *Regional Anesthesia* 1995; **20:** S13.
14. Freedman J, Li D, Jaskela M, Larsen B, Drasner K. Risk factors for transient neurologic symptoms after spinal anesthesia. *Anesthesiology* 1996; **85:** A741.
15. Zayas VM, Liguori GA, Chisholm MF. Transient radicular irritation (TRI) following spinal anesthesia with mepivacaine vs lidocaine in ambulatory surgery. *Anesthesiology* 1997; **87:** A829.

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CITATION CLASSIC

Commentary

Harrison GG. Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. *British Journal of Anaesthesia* 1975; **47**: 62–65.

Malignant hyperthermia (MH), in common with "scoline apnoea", is one of the pharmacogenetic conditions specific to anaesthesia. MH entered medical cognisance dramatically in 1960 with a letter to the *Lancet* by Denborough and Lovell,[1] although it should be remembered that Dr Jim Villiers was the anaesthetist who saved the young man's life[2] and referred him for further study. In less than 30 yr, an albeit uncommon but frequently fatal condition with a 70% mortality rate has been "controlled" to the extent that nowadays mortality is less than 2%. Gaisford Harrison can reasonably claim to be one of the few people who have enabled this truly amazing success.

In 1971, at the First International Symposium on MH, Toronto, the view was expressed that within 2 yr MH would be understood fully from the biochemical viewpoint. Certainly, by studying MH there has been a vast accumulation of knowledge and understanding of intracellular calcium homeostasis. Again, Harrison and co-workers[3] at the University of Capetown have been prominent in this work, using what has proved to be a substantial model of MH in MH susceptible breeds of swine.

Harrison's article in 1975 described the first use of the then comparatively new drug dantrolene sodium to control experimental MH in swine. MH in swine is an amazing condition. I well remember witnessing the "barnyard test" for MH when Harrison exposed individually a litter of piglets to 40% halothane delivered using a rubber funnel. Within 2 min, the susceptible piglets became rigid and rapidly developed cyanosis. The condition was reversed with difficulty by spraying the animals with cold water. The subtlety and efficacy of dantrolene should be seen in this context.

The major contribution of this article is the inspired use of dantrolene sodium. This drug was first described 7 yr earlier by Sneyder and co-workers[4] and was first used to control spasticity in hemiplegia in 1971.[5] Prior to dantrolene, many drugs had been tried, including steroids and procaine, but with little and variable success. One of the major problems with dantrolene was its insolubility in water and the need to use mannitol and sodium hydroxide to solubilize it.

The results of the first pig study are remarkable; figure 2 illustrates the explosive nature of MH in swine and the rapid and complete reversal with dantrolene in seven of the eight pigs. It is not clear why one of the pigs died, although the administered dose was the lowest used in the series. Presumably either the dose of dantrolene was insufficient or penetration of the contracted muscle was inadequate to reverse the metabolic changes induced by halothane.

After such a clear result it is difficult to understand why it took another 5 yr for dantrolene to become clinically available in the UK. In that period, deaths from MH continued to occur in approximately 24% of reactors. I remember G Harrison remarking in 1980 that MH should no longer be a clinical problem. Ironically, 1980, 1981 and 1982 were the worst 3 yr in the UK for deaths from MH. This clearly illustrates the point that merely having the right drug is not enough—its successful use depends on anaesthetists making a correct diagnosis, and using the drug at a time when the disease is reversible. This requires a combination of education and improved technology of monitoring.

This article deserves its "classic" label as it has altered our clinical practice permanently.

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References

1. Denborough MA, Lovell RRH. Anaesthetic deaths in a family. *Lancet* 1960; **2**: 45.
2. Denborough MA, Foster JA, Lovell RRH, Maplestone PA, Villiers JD. Anaesthetic deaths in a family. *British Journal of Anaesthesia* 1962, **34**: 395–396.
3. Berman MC, Harrison GG, Bull AB, Kench JE. Changes underlying halothane induced MH in Landrace pigs *Nature (London)* 1970; **225**: 653–655.
4. Sneyder HR, Davis CS, Bickerton RK, Halliday RP. 1 (5 arylfurfurylidene) amino hydantoins. A new class of muscle relaxants. *Journal of Medicinal Chemistry* 1967; **10**: 807–810.
5. Chyatte SB, Birdsong JH, Bergman BA. The use of dantrolene sodium in disorders of the central nervous system. *Southern Medical Journal* 1971; **64**: 830–834.

British Journal of Anaesthesia 1998; 81: 626–629

Br. J. Anaesth. (1975), 47, 62

CONTROL OF THE MALIGNANT HYPERPYREXIC SYNDROME IN MHS SWINE BY DANTROLENE SODIUM

GAISFORD G. HARRISON

SUMMARY

Experiments are described which demonstrate that dantrolene sodium effectively terminates the syndrome of malignant hyperpyrexia induced in susceptible swine by exposure to halothane. Dantrolene is also shown to block initiation of the syndrome of malignant hyperpyrexia by halothane in MHS swine. Therapeutic use of this drug in patients with anaesthetic-induced malignant hyperpyrexia appears to be indicated.

Anaesthetic-induced malignant hyperpyrexia is a rare, often fatal syndrome affecting man and the pig, which results from a genetic intrinsic functional defect within the muscle fibre (Relton, Britt and Steward, 1973; Harrison, 1973b). Rigor of muscle is its predominant clinical feature.

In 1967, Snyder and associates reported the synthesis of a series of hydantoins which proved to have muscle relaxant properties. One of these, dantrolene sodium* was extensively investigated and its pharmacological effects were demonstrated to follow an action on the intrinsic mechanism of muscle contraction. In addition, it was shown to act only on skeletal muscle and to have no effect on cardiac muscle or smooth muscle (Ellis et al., 1973). Because of this, the effects of dantrolene sodium on the syndrome of malignant hyperpyrexia induced by halothane in malignant hyperpyrexia susceptible (MHS) swine were investigated.

METHOD

In this investigation, use was made of an experimental protocol previously described (Harrison, 1973a). In MHS swine selected by reaction to halothane prescreening and estimation of serum c.p.k. levels, monitoring of vital parameters was established under initial ketamine or ketamine/thiopentone anaesthesia, followed by endotracheal intubation and maintenance of anaesthesia with nitrous oxide and oxygen. IPPV was provided when required by a Blease Pulmoflator.

Monitoring included:

(1) E.c.g.

(2) Observation of rigor (see fig. 1).

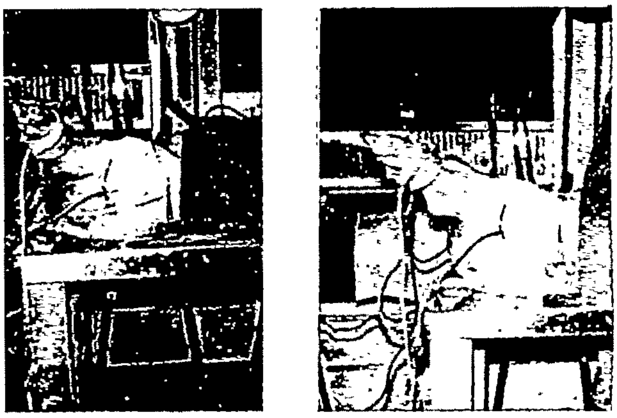

FIG. 1. MHS pig's hind legs before and after onset of rigor following halothane (note extension). The phenomenon may be recorded by attachment of the trotter by string over a pulley to a recording pen on a revolving drum. During rigor the muscle mass is palpably hard.

(3) Temperature measurement by means of a thermistor probe (Ellab, Denmark) inserted deep into the muscle mass of the thigh.

(4) Repeat sampling of mixed venous blood from a right atrial cannula.

Thereafter, the syndrome of malignant hyperpyrexia was initiated by the administration of halothane by IPPV commenced at a concentration of 2.5% and gradually reduced to 0.5% thereafter.

Once the hyperpyrexic syndrome was well established with marked muscle rigor, acidosis and an increase of temperature of 2°C or more, dantrolene sodium (0.5 mg/ml) was administered intravenously; a dosage of 1 mg/kg in early experiments was later increased to as much as 7–10 mg/kg.

The solubility of dantrolene is limited. The

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*1-([5-(p-nitrophenyl) furfurylidene] amino) hydantoin sodium hydrate synthesized by Norwich Pharmacal Company Laboratories, New York.

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formulation used in these experiments was that described by Castellion (1973, personal communication):

dantrolene sodium 300 mg
mannitol 26.640 g
sodium hydroxide 48 mg
water to make 600 ml

Blood samples for acid-base, c.p.k. and potassium estimations were taken:

(1) Immediately before exposure to halothane.

(2) When the syndrome was established.

(3) After administration of dantrolene.

Eight such experiments were undertaken using 5 pigs, the experiment being performed three times in one pig, twice in another and once each in the remaining 3 pigs.

It must be appreciated that in this somewhat crude and empiric (though effective) intact animal experiment, judgement of the moment at which to commence treatment was difficult, and precise criteria as to the degree of temperature increase could not be adhered to. The rate at which reactor pigs develop the syndrome differs. While it was desired that the syndrome be well enough established in terms of muscle rigor and increase in temperature, to render any response to dantrolene unequivocal, care had to be taken not to jeopardize the entire experiment by risking sudden death of an animal from cardiac arrest resulting from the concomitant acidosis and hyperkalaemia. In some experiments, not only was the moment of commencing dantrolene dictated by the onset of cardiac arrhythmia, but in two animals "Isoptin" 5 mg (Iproveratril, Knoll, Germany) (shown in previous experiments to have no effect on the syndrome (Harrison, 1972, unpublished data)) was used to control this before the administration of dantrolene. Once well initiated, the syndrome is independent of the concentration of halothane, which appears to act as a trigger (Berman et al., 1970). In five experiments, halothane was discontinued 8–18 min before administration of dantrolene, the syndrome continuing unabated with further increases in temperature of from 0.5 to 1.9°C. In three experiments halothane was continued for 2–4 min after commencement of dantrolene. In neither event did this appear to affect the outcome.

The only ancillary treatment generally applied was the administration of sodium bicarbonate following the onset of rigor. Ambient temperature during these experiments was 21–22°C and with one exception active cooling was not used. In the exception, ice blocks were applied to an animal after the temperature had decreased from 43.8°C to 41°C. Ambient temperature on this day was 25°C.

Complementary to the therapeutic use of dantrolene, its ability to block initiation of the hyperpyrexic syndrome by halothane in MHS pigs was also investigated in two experiments (a week apart) on a single fast reactor pig. In these experiments, following establishment of monitoring under initial ketamine / nitrous oxide / oxygen anaesthesia as described, and treatment of the animal with dantrolene 3 mg/kg, the animal was exposed to halothane inhalation for 90 min. Commencing at 2.5%, the halothane concentration was reduced over 30 min to 1%, at which concentration it was maintained.

RESULTS

The results of these experiments with details of the duration of the malignant hyperpyrexic syndrome before treatment, the actual increase in body temperature, maximum temperature attained, dose of dantrolene and final outcome in terms of survival, are presented in table I. A temperature and events chart of one experiment, typical of all the experiments, is reproduced in figure 2.

In the established syndrome of malignant hyperpyrexia in susceptible pigs, the administration of dantrolene caused:

(1) Rapid loss of muscle rigor commencing within 5 min and usually complete within 20 min.

(2) Immediate cessation of the increase in deep muscle temperature followed by a rapid decrease.

(3) Termination of the progressive, inexorable acidosis characteristic of the syndrome (Harrison et al., 1969) rendering easy the buffering of acidosis developed until the dantrolene administration.

All pigs, except the first, used in the 8 experiments survived. This first pig, after showing a dramatic initial response to what, in the light of subsequent experience, proved to be too small a dose of dantrolene, suffered a recurrence of the syndrome with subsequent death (see table I).

Dantrolene pretreatment of an MHS pig effectively blocked initiation of the hyperpyrexic syndrome by halothane, allowing exposure of the animal to inhalation for 90 min with impunity. The time period of 90 min was chosen arbitrarily as being a period six times in excess of the previously tested "reaction" time of the pig used.

TABLE I

Pig No. and weight	Resting c.p.k. A units/ml at 25°C (normal 0–50)	MH duration before dantrolene (min)	Increase in temp. (°C)	Max. temp. (°C)	Dose of dantrolene (mg/kg)	Temp. decrease in first 20 min (°C)	Final temp. (°C)	Outcome
170 70 kg	364	36	3.2	40.1	1	0.6	42.0	Died
168 120 kg	720	14	2.1	38.5	1	1.9	36.7	Survived
168 125 kg	817	40	2.4	38.8	2.5	2.2	36.4	Survived
182 30 kg	4932	38	3.6	42.2	7	2.0	38.4	Survived
180 39 kg	1480	18	2.0	40.2	6	1.4	38.2	Survived
180 40 kg	1340	21	2.0	40.5	10	1.5	38.4	Survived
180 44 kg	1440	36	3.2	40.0	7	2.6	37.3	Survived
74 30 kg	348	30	3.8	42.8	10	1.8	38.0 Ice packs	Survived

Different weights recorded for the same pig used more than once reflect weight gain with time.

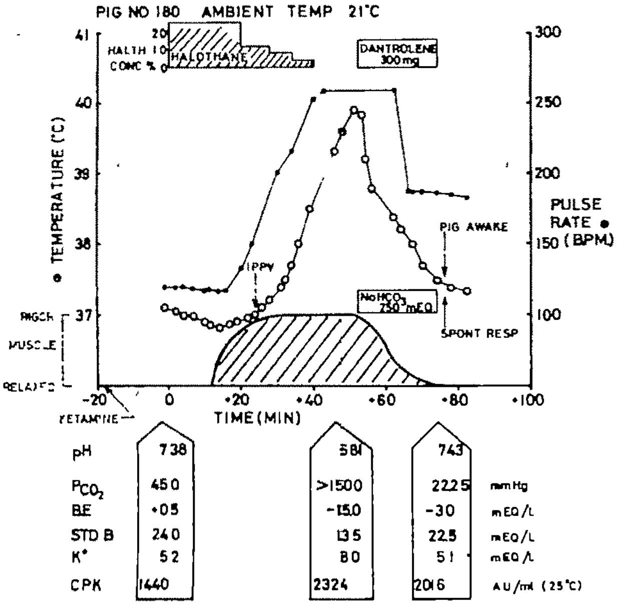

FIG. 2. Temperature (deep muscle) and events chart of typical experiment on MHS pig weighing 45 kg. Dantrolene administered as i.v. drip infusion for duration of square so marked. Biochemical values from mixed venous blood.

DISCUSSION

Untreated, the developed syndrome of malignant hyperpyrexia in pigs has a mortality rate of 100% (Harrison et al., 1969). While earlier work has demonstrated that it was possible to reverse the syndrome with procaine, especially if it was administered early enough (Harrison, 1971), the three out of five (60%) mortality for the established syndrome in pigs so treated described in this paper, has continued in our subsequent animal experiments. To date, procaine is the only drug that has been shown to have any effect on the established syndrome.

These experiments demonstrate that dantrolene has the property of relaxing the muscle rigor which characterizes malignant hyperpyrexia in the pig, and that concomitantly the excess heat and acid production cease. A survival rate of 100% was achieved in the last seven of eight experiments. In contrast to procaine, dantrolene has no effect on the myocardium, a factor which permits its use up to the limits of therapeutic effectiveness.

The pharmacology and toxicology of dantrolene have been extensively investigated in humans (Basmajian and Super, 1973; Chyatte and Birdsong, 1971; Chyatte, Birdsong and Bergman, 1971; Herman, Mayer and Newcombe, 1972) and it has been used extensively in the management of conditions characterized by muscle spasticity. The experiments reported here indicate that dantrolene should prove to be a most effective therapeutic agent in the treatment of malignant hyperpyrexia in humans.

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REFERENCES

Basmajian, J. V., and Super, G. A. (1973). Dantrolene sodium in the treatment of spasticity. *Arch. Phys. Med. Rehabil.*, **54**, 60.

Berman, M. C., Harrison, G. G., Bull, A. B., and Kench, J. E. (1970). Biochemical changes associated with malignant hyperpyrexia induced by halothane in susceptible pigs. *Nature (Lond.)*, **225**, 653.

Chyatte, S. B., and Birdsong, J. H. (1971). The use of dantrolene sodium in disorders of the central nervous system. *South. Med. J.*, **64**, 830.

—— —— Bergman, B. A. (1971). The effects of dantrolene sodium on spasticity and motor performance in hemiplegia. *South. Med. J.*, **64**, 180.

Ellis, K. O., Castellion, A. W., Honkomp, P. L. J., Wessels, F. L., Carpenter, J. F., and Halliday, R. P. (1973). Dantrolene, a direct acting skeletal muscle relaxant. *J. Pharm. Sci.*, **62**, 948.

Harrison, G. G. (1971). Anaesthetic-induced malignant hyperpyrexia—a suggested method of treatment. *Br. Med. J.*, **3**, 454.

—— (1973a). The effect of procaine and curare on the initiation of malignant hyperpyrexia; in *International Symposium on Malignant Hyperthermia* (eds. Gordon, R. A., Britt, B. A., and Kalow, W.), p. 271. Springfield, U.S.A.: Charles C. Thomas.

—— (1973b). Recent advances in an understanding of malignant hyperpyrexia. *Anaesthesist*, **22**, 373.

—— Saunders, S. J., Biebuyck, J. F., Hickman, R., Dent, D., Weaver, V., and Terblanche, J. (1969). Anaesthetic-induced malignant hyperpyrexia and a method for its prediction. *Br. J. Anaesth.*, **41**, 844.

Herman, R., Mayer, N., and Newcombe, S. A. (1972). Clinical pharmacophysiology of dantrolene sodium. *Am. J. Phys. Med.*, **51**, 296.

Relton, J. E., Britt, B. A., and Seward, D. J. (1973). Malignant hyperpyrexia. *Br. J. Anaesth.*, **45**, 269.

Snyder, H. R., Davis, C. S., Bickerton, R. K., and Halliday, R. P. (1967). 1 (5-Arylfurfurylidene) amino hydantoins. A new class of muscle relaxants. *J. Med. Chem.*, **10**, 807.

CONTROLE DU SYNDROME D'HYPERPYREXIE MALIGNE (DANS LES SUIDES MHS) AU MOYEN DU SODIUM DE DANTROLENE

RESUME

On décrit certaines expériences qui démontrent que le sodium de dantrolène met fin effectivement au syndrome d'hyperpyrexie maligne provoqué par l'exposition à l'halothane chez les suidés prédisposés. On montre également que le dantrolène bloque la manifestation initiale du syndrome d'hyperpyrexie maligne par l'halothane dans les suidés MHS. L'usage thérapeutique de ce remède semble indiqué pour les patients atteints d'hyperpyrexie maligne provoquée par un anesthésique.

BEKÄMPFUNG DES MALIGNEN HYPERPYREXIESYNDROMS (BEI MHS-SCHWEINEN) MIT DANTROLEN-NATRIUM

ZUSAMMENFASSUNG

Es werden Untersuchungen beschrieben, welche ergaben, daß Dantrolen-Natrium das bei empfänglichen Schweinen durch Halothan-Einwirkung hervorgerufene maligne Hyperpyrexiesyndrom wirksam kupiert. Außerdem konnte gezeigt werden, daß sich bei MHS-Schweinen die Auslösung eines malignen Hyperpyrexiesyndroms durch Halothan mit Dantrolen blockieren läßt. Das Mittel scheint sich also zur Behandlung von Narkose-bedingten malignen Hyperpyrexiesyndromen zu eignen.

CONTROL DE LOS SINDROMES DE HIPERPIREXIA MALIGNA (EN CERDOS CON SHM) POR SODIO DANTROLENICO

SUMARIO

Se describen los experimentos que demuestran que el sodio dantrolénico acaba eficazmente con el síndrome de hiperpirexia maligna, inducido en un cerdo, suceptible a ella, por exposición a halotano. Se muestra también que el Dantroleno bloquea la iniciación del síndrome de hiperpirexia maligna por halotano en cerdos con SHM. Parece ser apropiado el uso terapéutico de esta droga en pacientes con hiperpirexia maligna, de inducción anestésica.

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ABSTRACTS

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All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Patient controlled morphine analgesia (PCA morphine) in cadaveric renal transplant recipients: does morphine-6-glucuronide accumulate?

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Morphine is metabolized in the liver to two main metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Failure to excrete M6G in azotaemic states is believed to be the cause of delayed respiratory depression which can occur up to 24 h after the most recent morphine dose.[1] The excretion of M6G following a single bolus dose of morphine to patients receiving live-related renal grafts closely follows the onset and degree of graft function.[2] However, PCA morphine provides the mainstay of post-renal transplant analgesia throughout most of Great Britain. Our pilot study compares the accumulation of M6G in cadaveric renal graft recipients and general surgery patients with normal renal function where both groups received PCA morphine postoperatively.

Written informed consent was obtained from 10 patients, four undergoing general abdominal surgery and six receiving cadaveric renal transplants. All received a standardized anaesthetic including a 10 mg bolus of morphine at induction. Postoperatively, all patients received a PCA pump which gave a 1 mg bolus of intravenous morphine with a five minute lock-out time in the control population and a 15 minute lockout in the transplant group. Twenty one blood samples were collected from each patient at predetermined intervals over the 72 h following surgery. High performance liquid chromatography was performed on the samples and plasma concentrations of M6G determined. The total amount of morphine given by each sampling time was recorded, curves of plasma M6G against time constructed, and AUC mg^{-1} morphine calculated for both study and control populations (table 1). The results were compared using the Mann–Whitney U test. Renal function was assessed for each patient using twice daily serum creatinine measurements.

Significant ($P<0.02$**) accumulation of M6G was seen in the transplant group compared with the control population despite the fact that four of the six transplants had sufficient primary graft function to require no further haemodialysis after transplantation. The plasma M6G values in four transplant recipients reached those associated with respiratory depression in previously reported cases, but no such complications were noted in any of our patients.

Table 1 Comparison of control and transplant patients. AUC = area under the curve

	Control patients				Transplant recipients					
Variable	A	B	C	D	A	B	C	D	E	F
AUC M6G 0–72 h (nmol l^{-1} h^{-1})	2372	2740	3274	21759	50347	36288	15235	11777	23554	38284
Total morphine 0–17 h (mg)	78	91	164	402	57	58	64	51	80	68
AUC mg^{-1} morphine	30.4	30.1	20.0	54.1	883.3	677.4	238.0	230.9	294.4	563.0
Median AUC mg^{-1}	30.2**				428.7**					

AUC, area under the curve.

Acknowledgement

This work was supported by the R and D Fund, Western Infirmary, Glasgow.

Keywords: analgesics opioid, morphine; kidney, transplantation

References

1. Osborne RJ, Joel SP, Slevin ML. *British Medical Journal* 1986; 292: 1548–1549.
2. Osborne RJ, Joel SP, Grebenik K, Trew D, Slevin ML. *Clinical Pharmacology and Therapeutics* 1993; 54: 158–167.

A puzzle in propofol loss rates from tissue samples in sheep

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This puzzle arose out of a study to determine tissue concentrations and tissue/blood partition coefficients for propofol in sheep. The aim of this presentation is to seek help in explaining a surprising pattern of loss rate of propofol from the stored tissue samples.

A bolus of propofol, 10 mg kg^{-1} body mass, was given intravenously to each of six sheep; cardiac arrest was induced with potassium chloride at 2–5 min; samples of tissue were taken from brain, heart, kidney, liver, lungs, spleen, and muscle. These were stored in plastic bags at −20°C and analysed for propofol content after intervals of 6, 12, and 18 months. In another eight sheep, propofol was infused intravenously at 1 ml min^{-1} for 2 h; arterial concentrations were measured at intervals; cardiac arrest was induced and tissue samples were taken and stored as before, but analyses were made within one month and again after 6 to 10 months.

Since the "unit of investigation" is the tissue sample, a linear regression was fitted to the change of concentration with time in each sample.[1] This was done in a single analysis which showed that the fit was 30% better in terms of log concentration than of actual concentration, indicating that the decline of concentration was exponential rather than linear. Analysis of variance of the resulting slopes led to the pattern of loss rates in table 2. These were applied

Table 2 Loss rates of propofol from tissue samples

Tissue	Log (conc) per day		Loss rate (% per day)		Half life (days)
	Mean	SE	Estimate	95% CI	
Bolus: non-spleen	–0.001273	0.000161	0.293	0.22 to 0.37	236
spleen	0.000342	0.000263	–0.079	–0.20 to 0.04	–881
Infusion: all tissues	–0.000119	0.000150	0.027	–0.04 to 0.10	2525

Conc, concentration in $\mu g\ g^{-1}$; CI, confidence interval.

to the tissue concentration measurements to determine the fitted concentration at "day 0" – except that zero loss rate was used instead of the two non-significant loss rates. In the infusion experiments, the day 0 concentrations were divided by the fitted arterial concentration at the time of cardiac arrest to yield tissue/blood partition coefficients.

One possible mechanism of loss is evaporation. If that were the case, half life should be proportional to the solubility of propofol in the tissues; but there was nothing exceptional about spleen in terms of concentration in the bolus experiments or partition coefficient in the infusion experiments. Also it seems inconceivable that solubility in tissues in the infusion experiments was 10 times that in the bolus experiments. Another possibility is degradation of the propofol. There is wide overlap of concentrations of propofol between the three conditions in table 2, but the amount of its vehicle, Intralipid, would be much greater in the infusion experiments, and somewhat greater in spleen than other tissues because of the very high blood content of spleen. Could Intralipid have some kind of preservative action? Comments and alternative explanations will be welcomed.

Acknowledgement

Supported by the Wellcome Trust, the Perry Foundation and Zeneca Pharmaceuticals.

Keywords: anaesthetics i.v., propofol; sheep

References

1. Altman DG. *Practical statistics for medical research.* London: Chapman and Hall, 1991: 426–433.

Closed loop computer controlled sedation with propofol

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Automated control systems are widely used in critical applications; however, their use in medical care is relatively unusual. We have developed a system for automatic control of sedation and tested it in seven human volunteers.

Bifrontal raw electroencephalogram (EEG) and derivatives including the bispectral index (BIS V3.12) were recorded and logged using an Aspect A1000 monitor and a personal computer with custom written software (C Borland). A proportional integral derivative (PID) controller and a four-compartment pharmacokinetic/pharmacodynamic (PK/PD) model automatically adjusted target effect site propofol concentration by controlling an infusion pump (Graseby 3400) to maintain a constant value of BIS. After a 10 minute baseline EEG recording without sedation, the BIS target was set to 65 for a period of 25 minutes, after which sedation was discontinued "Open loop" target controlled infusion was used for the first 2.3 minutes. The initial target effect site propofol concentration (Ce) was calculated from the BIS target using the following formula adapted from Doi and colleagues[1] BIS=–12.837Ce+93.582.

Subsequently the PID controller adjusted the effect site target automatically—that is, a "closed loop." After 15 minutes of sedation subjects were stimulated with a nerve stimulator applied to the wrist (30 mA for 2 min followed by 40 mA for 3 min). Satisfactory sedation was achieved in all subjects (fig 1).

Attainment of the BIS target was rapid but three subjects were initially oversedated (minimum BIS values during minutes 0–5 for these subjects were 48.3, 34.9, and 41.5). The measured BIS in seven subjects between 2.3 and 15 minutes ("closed loop" control, no stimulation) was 65.2 (5.8) (mean (SD)), and between 15 and 20 minutes (during stimulation), 66.3 (6.8).

Our system automatically established and maintained sedation in volunteers. Clinical application will require further evaluation in patients.

Keywords: anaesthetics i.v., propofol; model, computer

Acknowledgements

We thank Graseby Medical Ltd for the loan of an infusion pump and Dr Steven Shafer for some source C code from STANPUMP.

Reference

1. Doi M, Gajraj RJ, Manzaridis H, Kenny GNC. *British Journal of Anaesthesia* 1997; 78: 180–184.

A comparison of vasoactivity between levobupivacaine and bupivacaine

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Stereoisomerism and drug concentration both influence the vasoactive properties of local anaesthetic agents. Determination of

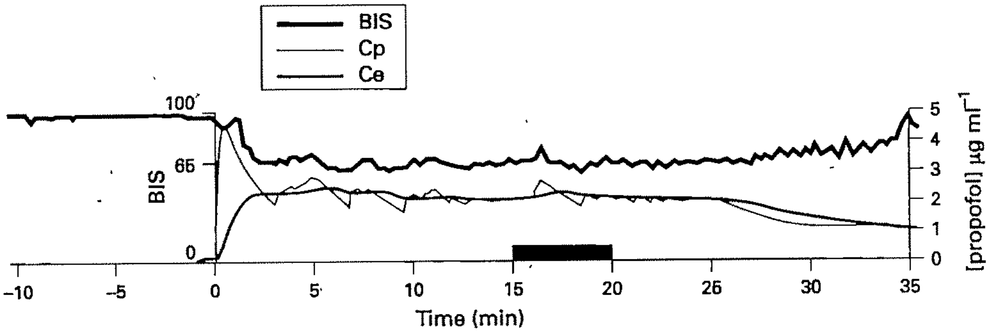

Figure 1 Bispectral index (BIS), predicted plasma propofol concentration (Cp), and effect site propofol concentration (Ce) in a single subject. The period of stimulation is indicated by a bar.

the effect of a local anaesthetic on the vasculature can be achieved using intradermal testing[1] Quantification of that effect can be obtained with laser Doppler perfusion imaging (LDPI), a rapid non-invasive technique enabling detailed analysis of skin blood flow patterns. The LDPI (Lisca Developments, Sweden) can scan an area of approximately 120×120 mm, thus enabling skin blood flow changes at each site to be compared simultaneously. The device is linked to computer software for image display and analysis. We have used this technique to compare the vasoactivity of racemic bupivacaine and levobupivacaine when given intradermally.

A double blind, randomized, placebo controlled study was performed on 11 male non-smoking volunteers. Observations were recorded in a room thermostatically controlled at 22°C. Five sites were randomly allocated to the volar surface of each forearm, with a minimum separation of 3 cm. One site was untreated and served as baseline. At the control site, 0.1 ml 0.9% sodium chloride was injected intradermally through a 30 gauge needle. In the remaining eight sites, 0.1 ml each of 0.75%, 0.5%, 0.25%, and 0.125% levobupivacaine and the same concentrations of racemic bupivacaine were given. Baseline skin blood flow was determined before giving the injections. Subsequent measurement of skin blood flow was made at 2.5, 10, 20, 40, 60, and 90 minutes after injection. Total response (flux signal, volts) over time of each dose of the two drugs with respect to saline was evaluated by calculating an index of the area under each curve. These results are summarized in fig 2. The two significance levels are the results of a two way repeated measures analysis of variance, testing the difference between each dose and each drug, with a P value <0.05 indicating a 95% confidence of difference. At all concentrations tested levobupivacaine showed greater vasoconstrictor activity than bupivacaine ($P=0.019$), with a maximum difference at higher concentrations. A decrease in skin blood flow with respect to saline was observed with levobupivacaine at concentrations less than 0.25%.

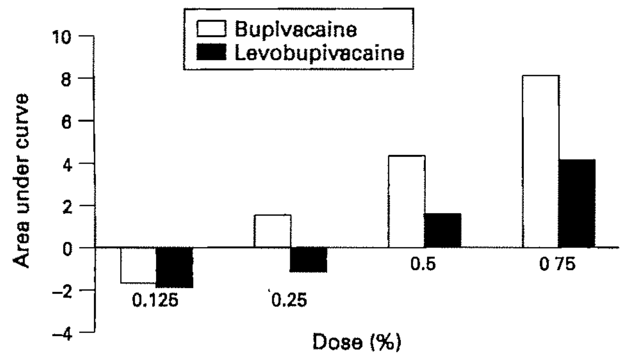

Figure 2 Response compared with saline. Significance levels: $P=0.019$ for drug; $P=0.001$ for dose.

Keywords: anaesthetics local, bupivacaine; pharmacokinetics, stereoisomers; skin, blood flow

Reference

1. Aps C, Reynolds F. *British Journal of Clinical Pharmacology* 1978; **6**: 63–68.

Methaemoglobinaemia after supraclavicular block with prilocaine in patients with renal failure

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Prilocaine is thought to offer a good balance between onset, duration, and safety for the large volumes used for brachial plexus anaesthesia. In doses well in excess of 600 mg or 8 mg kg^{-1} it can produce methaemoglobinaemia. Subclinical methaemoglobinaemia also occurs.[1] The methaemoglobinaemia is caused by o-toluidine, a renally excreted metabolite of prilocaine. We studied the incidence and time course of methaemoglobinaemia in patients with renal failure who had supraclavicular block using prilocaine.

We studied 17 patients requiring arteriovenous fistula formation. Supraclavicular block was established using a nerve stimulator and prilocaine 7 mg kg^{-1} to a maximum dose of 600 mg. Venous blood was taken before performing the block, and then at 30, 60, 90, 120, 240, 360, and 480 minutes. Methaemoglobin levels were measured using a Ciba Corning 270 cooximeter. Prilocaine and o-toludine levels were determine by high performance liquid chromatography.[2]

An increase in the percentage of methaemoglobin with time was found, as shown in fig 3, with peak values occurring at 4 h. Peak methaemoglobin showed a non-significant correlation with (a) the peak prilocaine level (Spearman correlation coefficient $r=0.14$, $P=0.6$) or (b) the peak o-toludine level (Spearman correlation coefficient $r=0.3$, $P=0.25$).

Using recommended doses of prilocaine we found levels of methaemoglobin which could be clinically significant in medically compromised patients.

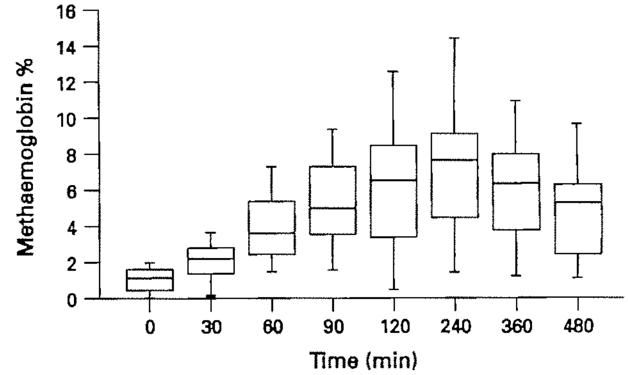

Figure 3 Percentage methaemoglobin at time after performance of supraclavicular block. Shown are medians, 25th and 75th centiles (bars), and ranges.

Keywords: complications, methaemoglobinaemia; anaesthetics local, prilocaine

References

1. Bellamy MC, Hopkins PM, Halsall PJ, Ellis FR. *Anaesthesia* 1992; 47: 1084–1085.
2. Klein J, Fernandes D. *Journal of Chromatography* 1994; 655: 83–88.

The effects of glycinergic block on sensory transmission and on the action of halothane in the urethane anaesthetized rat

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Halothane has been shown to potentiate the responses, both of isolated medullary neurones and of recombinant glycine receptors expressed in *Xenopus* oocytes, to the inhibitory neurotransmitter glycine.[1] It was suggested that potentiation of glycinergic transmission might play a role in the process of general anaesthesia.

The aim of this study was to examine the role of glycine in quantifiable processes of general anaesthesia in vivo. Female rats were anaesthetized with urethane (1.25 g kg^{-1} intraperitoneally (ip), weight 190–210 g; n=8). The effect of strychnine (0.1 mg kg^{-1} ip, approximately 4×10^{-7} M in body water), a potent antagonist of glycinergic transmission, was measured on the electrocorticogram, on peripherally evoked cerebral, cortical, and thalamic single cellular responses, and on respiration (after Angel[2]). Halothane (1%) was given alone, and in conjunction with strychnine, in order to assess any specific glycinergic role in its mechanism of action.

Strychnine caused no statistically significant changes in the power spectral content of the electrocorticogram (Student's paired two tailed t test; n=5) nor in respiratory rate and tidal volume (n=4). Early components of the cortical mass evoked response were not significantly altered following administration of strychnine: latency 3.45 (0.21) ms (mean (SD)), initial positive wave 100(7.2)%, initial negative wave 100(29.9)% before strychnine, compared with 3.48 (0.17) ms, 98.7(8.2)%, and 101.1(19.7)%, respectively, following strychnine administration (Student's paired, two tailed t test; n=5). Strychnine likewise failed to alter the latency and probability of evoked responses by single cells in the cortex (n=5) and ventrobasal thalamus (n=3).

The effect of halothane on these indices of central nervous system responsiveness was not significantly altered by administration of strychnine. In the absence of strychnine, for example, 1% halothane depressed the cortical mass evoked response such that the latency increased by 0.69 (0.31) ms, the initial positive wave decreased to 89.5(16.7)% and the initial negative wave to 54.1(9.2)%. In the presence of strychnine, halothane increased the latency by 0.98 (0.37) ms and reduced the initial positive and negative inflections to 87.7(15.9)% and 54.0(12.6)%, respectively. These changes were not significant (Student's paired, two tailed t test; n=4).

Blockade of glycinergic transmission failed to alter these indicators of anaesthetic depth. These data suggest that it is unlikely that the state of anaesthesia is dependent upon alteration in glycinergic transmission above the level of the spinal cord.

Acknowledgement

RHA was supported by a postgraduate scholarship from the University of Sheffield.

Keywords: nerve, transmission; anaesthetics volatile, halothane

Reference

1. Downie DL, Hall AC, Lleb WR, Franks NP. *British Journal of Pharmacology* 1996; **118**: 493–502.
2. Angel A. *Experimental Physiology* 1991; **78**: 1–38.

Steady state halothane anaesthesia oscillates between two states of electrocortical arousal

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It has previously been reported that urethane anaesthetized rats oscillate randomly between two states of electrocortical activity, high voltage low frequency (HVLF) and low voltage high frequency (LVHF).[1] It has now been established that this is also the case in halothane anaesthetized rats. Six female rats (Sheffield strain) anaesthetized with 1.3% halothane were used. The forepaw was stimulated using supramaximal electrical stimuli and the electrocorticogram, cerebral evoked responses, and responses of single cells in cortical layer IV were recorded. During 1.3% halothane anaesthesia two phases of electrocortical activity can be seen. Power spectral analysis of the electrocorticogram showed that one phase was characterized by relative increase in power of higher frequencies (≥13 Hz); the other showed a relative increase in the power of lower frequencies (≤4 Hz). Hence the two states can be designated LVHF and HVLF respectively (fig 4). These states were accompanied by changes in both cortical evoked responses and cellular responsiveness to peripheral stimuli. In LVHF the cortical cells showed short latency, high probability firing in response to the stimulus, and the cortical evoked response is of short latency with a larger amplitude initial positive (Pi) and negative wave (Ni) (fig 4). In HVLF the cortical cells showed longer latency, lower probability firing, and the evoked response was of increased latency with Pi and Ni of decreased amplitude. The changes in electrocortical activity were also accompanied by changes in the rate of respiration which increased during LVHF and decreased during HVLF.

Thus halothane anaesthesia, like urethane anaesthesia, is not a steady state condition but switches between more aroused (LVHF) and less aroused (HVLF) states. The former is characterized by short latency cortical responses of increased magnitude, increased respiration rate, and higher frequency electrocorticogram than the latter.

Acknowledgement

SCW holds a University of Sheffield PhD studentship.

Keywords: anaesthetics volatile, halothane; measurement techniques, electrocorticography

Reference

1. Angel A, Dodd J, Gray JD. *Journal of Physiology* 1976; **259**: 11–12P.

The effect of conduction block on spinal ir-galanin release in the neuropathic rat

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Galanin, a neuropeptide with an increased inhibitory role after nerve injury, is normally found in the spinal cord, with little in dorsal root ganglia cells. After peripheral nerve injury, galanin concentrations increase in small to medium sized dorsal root ganglion cells, with a corresponding rise in central release in the superficial dorsal horn of the spinal cord, ipsilateral to a sciatic nerve injury.[1] The stimulus for this spontaneous immunoreactive (ir) galanin release in neuropathic rats is not known, but it may be related to

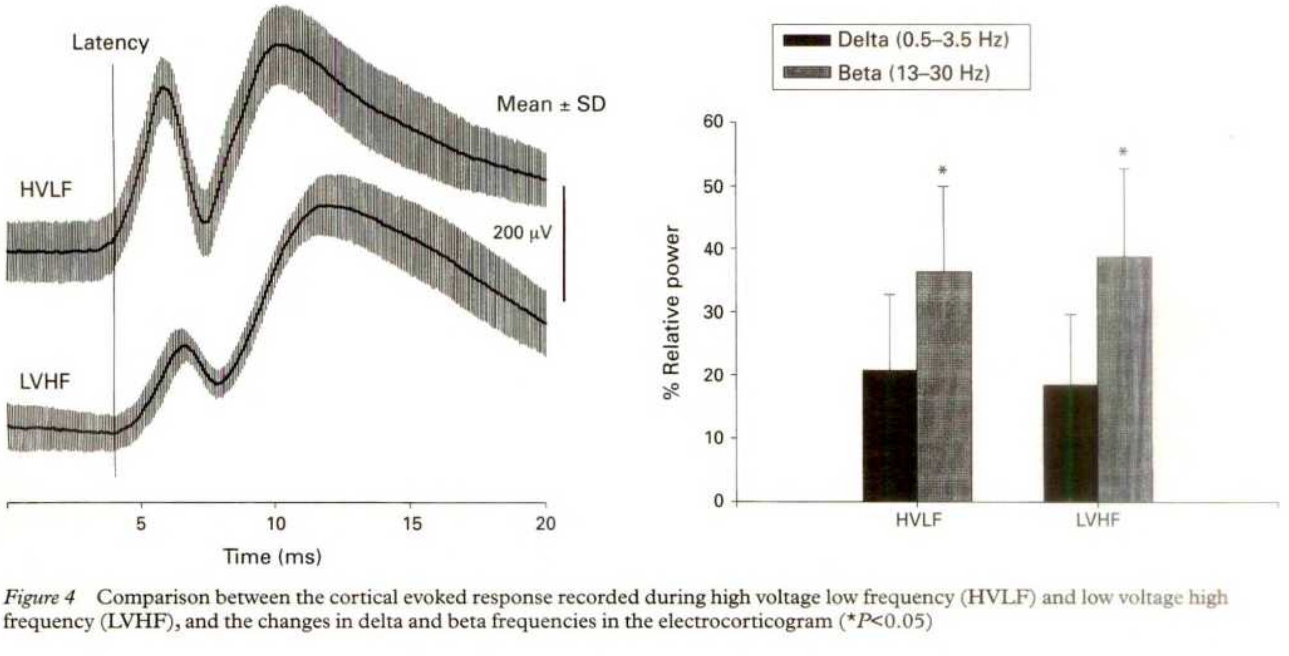

Figure 4 Comparison between the cortical evoked response recorded during high voltage low frequency (HVLF) and low voltage high frequency (LVHF), and the changes in delta and beta frequencies in the electrocorticogram (*$P<0.05$)

spontaneously occurring ectopic discharges arising after nerve injury.[2] The aim of this study, therefore, was to determine the effect of blocking all neuronal input from the injured nerve on spinal release of ir-galanin.

Male Wistar rats (n=12), with evidence of neuropathic pain were studied 10–14 days after a chronic constriction injury of one sciatic nerve.[3] Galanin antibody coated microprobes were inserted 2.25 mm into the spinal cord of urethane (1.25 g kg^{-1}) anaesthetized rats and left in situ for 15 minutes. They were then washed, incubated in ^{125}I galanin, and the tips placed on x ray monoemulsion film for 8–10 d. An autoradiographic image was obtained for each probe which was analysed using a computerized image analysis system. Localized areas of endogenous ir-galanin release were detected as decreases in optical density of the image. Significant differences (P<0.05) between means of selected groups were determined by Student's unpaired t test carried out at 30 µm intervals. Basal levels of ir-galanin release were determined, then amethocaine gel was applied proximal to the dorsal root ganglia, after which further galanin antibody-coated microprobes were inserted into the spinal cord.

Previous findings of an increased area of spontaneous ir-galanin release in the superficial dorsal horn ipsilateral to nerve injury were confirmed. After conduction block, although no change in ir-galanin release in the ipsilateral dorsal horn was found, there was an increase in the contralateral dorsal horn such that the previous side to side difference was no longer apparent. This contralateral action may be mediated either by supraspinal systems or intrinsic loops in the dorsal horn. Ongoing input from the injured nerve could be preventing increases in ir-galanin release, and may therefore play a role in the generation of spontaneous pain.

Acknowledgement

This work was funded by a BJA fellowship and a Wellcome Trust grant.

Keywords: nerve, transmission; model, rat; pain, experimental

References

1. Colvin LA, Mark MA, Duggan AW. *Brain Research* 1997; **766**: 259–261.
2. Kajander KC, Wakisaka S, Bennett GJ. *Neuroscience Letters* 1992; **138**: 225–228.
3. Bennett GJ, Xie YK. *Pain* 1988; **33**: 87–107.

Effects of opioids on sensory bupivacaine spinal block

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Systemic and intrathecal opioids increase the height[1,2] and delay the regression[3,4] of sensory block after subarachnoid anaesthesia. The mechanism of this synergistic effect is unclear and the aim of this randomized, controlled, double blind study was to investigate whether it occurs predominantly at a peripheral or a central site.

Thirty male patients, ASA grades I and II, scheduled for elective urological surgery under spinal anaesthesia were recruited. Patients taking regular analgesics or with CNS disorders were excluded from the study. Premedication consisted of temazepam 10 mg one hour preoperatively. Patients were allocated to one of three groups: group A – spinal solution (2.5–3 ml 0.5% bupivacaine+1 ml 0.9% saline), intravenous saline (1 ml) ; group B – spinal solution (2.5–3 ml 0.5% bupivacaine+1 ml fentanyl (50 µg)), intravenous saline (1 ml); group C – spinal solution (2.5–3 ml 0.5% bupivacaine+1 ml saline), intravenous fentanyl (50 µg). Lumbar puncture was performed by a standardized technique at L2–3 interspace. The intravenous solution was given simultaneously with the spinal injection. Midazolam 1 or 2 mg was given as clinically indicated for sedation. After 30 minutes sensory block to pinprick with a 22G short bevel needle and cold sensation with ethyl chloride spray was assessed at four separate lines drawn on the left side of the patient's body (posterior, middle, and anterior axillary lines and a line 5 cm anterior to the latter) to give an average baseline level. Naloxone 0.4 mg was given intravenously at this time, and after a further 10 minutes the sensory level was reassessed. Changes were recorded as cm deviation from the baseline level. Data were analysed by Kruskal–Wallis, Mann–Whitney, and Student's t test as appropriate.

Results are given in table 3. There were no differences in age, weight, or height between the three groups. The height of block in the three groups was indistinguishable. Naloxone decreased the level of sensory block in the intravenous fentanyl group. There was no decrease in the intrathecal fentanyl and saline groups.

Table 3 Changes in the level of sensory block (cm) from the baseline determination at 10 min after treatment with naloxone

	A (it/iv saline) (n=9)	B (it fentanyl) (n=10)	C (iv fentanyl) (n=11)
Change in level (cold)	−0.7 (-8.1, 3.3)	+0.9 (-0.9, 4.3)	−5.1*† (-17.9, 1.2)
Change in level (pin prick)	−0.7 (-3.9, 2.0)	0.0 (-0.8, 0.7)	−3.1*† (-11.4, 0.5)

Values are median (range); it, intrathecal; iv, intravenous.
Intergroup comparisons: *P<0.05 (C *v* A); †P<0.01 (C *v* B).

Keywords: analgesics opioid, fentanyl; anaesthetics local, bupivacaine

References

1. Sarantopoulos C, Fassoulaki A. *Anesthesia and Analgesia* 1994; **79**: 94–97.
2. Adkisson GH, Waters JH, Burger GA. *Anesthesia and Analgesia* 1993; **76**: S2.
3. Singh H, Yang J, Thornton K, Giesecke AH. *Canadian Journal of Anaesthesia* 1995; **42**: 987–991.
4. Henderson DJ, Jones G. *British Journal of Anaesthesia* 1995; **74**: 610–611.

The effect of nitrous oxide on transmission in the dorsal column pathway in the urethane anesthetized rat

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We have reinvestigated the effect of nitrous oxide upon sensory transmission. It has previously been reported that nitrous oxide acts as a conventional general anaesthetic upon the cerebral evoked response to forepaw stimulation in the rat.[1] The data presented here show that this conventional action of nitrous oxide is often phasic. Female rats (n=26, Sheffield strain) anaesthetized with intraperitoneal urethane (1.25 g kg^{-1}) were used to study the effect of nitrous oxide upon the electrocorticogram, cerebral evoked responses, and responses from single cells in the ventrobasal thalamus and layers IV, V, and VI of the cerebral cortex to electrical stimulation of the forepaw. In 18 animals nitrous oxide showed a phasic effect which was never seen with approximately equipotent doses of halothane (fig 5).

This "switch" in behaviour occurred at 13.61 (6.08) min (mean (SD)) after application of 80% nitrous oxide and 14.17 (5.70) min after application of 50% nitrous oxide. It was not constant in individual animals. The phasic effect was also seen in the electrocorticogram and in 11 layer IV, five layer V, and seven layer VI cortical cells, and in two ventrobasal thalamic cells. All of these cells showed a dose dependent increase in latency and a decrease in probability of response in the anaesthetic phase of the nitrous oxide effect, similar to conventional agents. After the switch, cell behaviour became stabilized at a higher level of probability and increased latency of response compared with the anaesthetic phase but the probabilities of response and latencies did not return to pre-nitrous oxide values until the nitrous oxide was switched off. During prolonged exposure to nitrous oxide (2–4 h) cerebral evoked responses switched randomly and spontaneously between the two states. The mechanisms underlying this effect are under investigation.

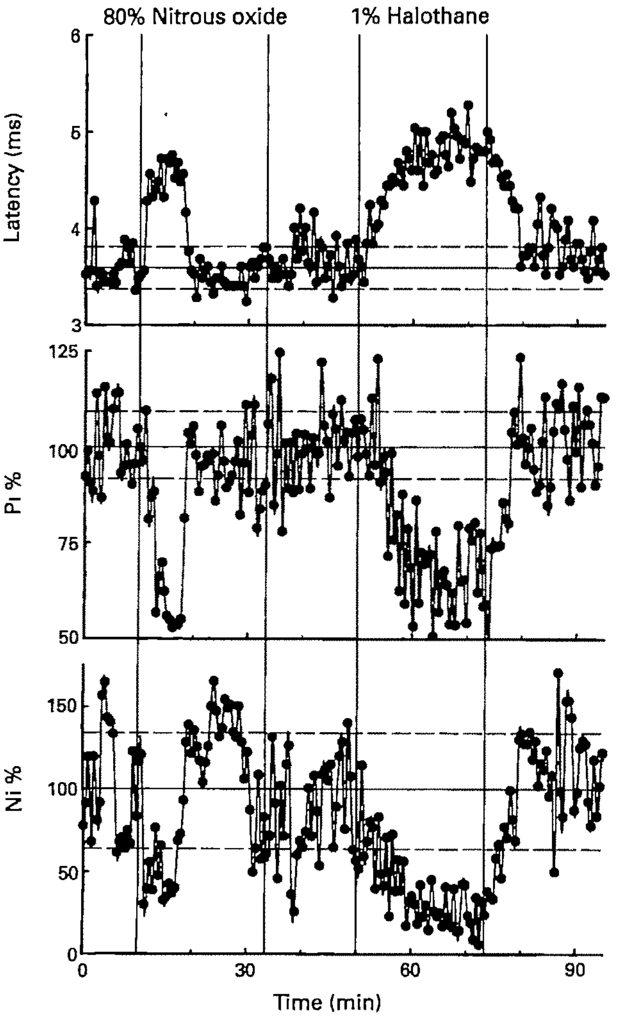

Figure 5 Effect of approximately equipotent doses of nitrous oxide and halothane on the latency, initial positive wave (Pi), and initial negative wave (Ni) of averaged cerebral evoked responses (n=50) to electrical stimulation of the contralateral forepaw at a rate of 1 s^{-1}.

Acknowledgement

SCW holds a University of Sheffield PhD studentship.

Keywords: anaesthetics gases, nitrous oxide; rat; brain, evoked potentials

Reference

1. Angel A, Gratton DA. *Journal of Physiology* 1980; 302: 2P.

In vitro study of the effect of vessel compliance on the estimated resistance using Doppler indices

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Pulsatility index (PI), resistance index (RI), or the ratio of perfusion pressure (P) and Doppler flow velocity (FV) are used to assess vascular resistance[1] The aim of this study was to examine the effect of a change in the compliance of the insonated vessel on these variables.

An in vitro pulsatile flow model was constructed using artificial vessels and perfusion media This included a computer controlled pump capable of generating flow waves of a predetermined pulse rate and diastolic and systolic flow velocities The circulatory circuit incorporated a Windkessel, a bypass limb with variable resistance, and an insonated limb with a variable peripheral resistance bed. The flow velocity profile of an internal carotid artery was simulated in the insonated limb. Peripheral resistance of this limb was adjusted, altering the flow through the insonated vessel, over a range of values. Pulse rate, driving pressure, and the total flow (bypass+insonated limbs) in the circuit was kept constant PI, RI, FV, and flow in the insonated vessel (F) were recorded during established steady states over a range of resistances (0 3–1.9 R units) in the insonated limb (compliance 0.25% mm Hg^{-1}). The experiment was repeated after replacing a section of the insonated limb with a rigid vessel of the same internal diameter (compliance 0.07% mm Hg^{-1}). Actual resistance in the insonated limb was estimated by calculating the ratio between P and F. Regression analysis was used to study the relationship between the change in the actual resistance (P/F) and the corresponding changes in the resistance estimated by P/FV, PI, or RI as measured by Doppler ultrasound, for the two vessels of different compliance. Regression equations and r^2 values for these relations are shown in table 4.

Estimations of the resistance with PI and RI were not affected by the change in the compliance of the insonated vessel. However, P/FV consistently estimated a higher resistance for the rigid vessel over the full range of the change in the actual resistance. Extrapolations from in vitro models to human physiology are at best approximations. We suggest that the changes in vessel wall compliance should be taken into consideration for the Doppler estimation of vascular resistance in clinical practice or research

Table 4 Regression analysis data

	Compliant Regression equation	r^2	Rigid Regression equation	r^2
P/FV	0.33P+9.12P/F	0.89	0.37P+15 70P/F	0.96
PI	0.14+57.50/F	0 95	0.03+54.90/F	0.91
RI	0.46+4.36/F	0.72	0.39+5 93/F	0.88

Acknowledgement

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Keywords: blood, flow; measurement techniques, Doppler

Reference

1. Legarth J, Thorup E. *Scandinavian Journal of Clinical Investigation* 1989; 49: 451–457.

Magnetic resonance imaging of the vertebral canal before and after central nerve block: is there any subclinical bleeding?

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Clinically significant thecal compression by extradural haematoma after central nerve blockade is very uncommon, with an estimated incidence of 1/150 000 after epidural block and 1/220 000 following spinal block.[1] However, there is still concern that this catastrophic complication may occur after central nerve blockade, particularly in patients who have received drugs which affect normal coagulation. In this study the vertebral canal was examined by magnetic resonance imaging (MRI) before and after central nerve blockade to identify subclinical epidural bleeding in low risk and high risk patient groups.

Two groups of 20 patients scheduled for elective vascular surgery were recruited after giving informed consent. The "low risk" (group 1) patients were ASA I–II (age <60 years) and undergoing varicose vein surgery under spinal anaesthesia. Patients who had taken any drug which could affect normal coagulation within the preceding seven days were excluded. Spinal anaesthesia was performed using a 25G Whitacre pencil point needle and 2.5 ml of 0.5% hyperbaric bupivacaine. The "high risk" (group 2) patients were ASA II–IV (age >60 years) and undergoing lower limb arterial reconstructive procedures under epidural anaesthesia with catheter insertion. Most of these patients were on aspirin preoperatively and they all received 3000–5000 units of heparin intravenously before arterial clamping during surgery An 18G Touhy needle was used to insert a similarly sized epidural catheter, and the block was established using 15–20 ml of 2% lidocaine. Epidural catheters were removed the morning after surgery at least one hour before any subcutaneous heparin was given for deep venous thrombosis prophylaxis. T1 and T2 weighted saggital and axial MR lumbar spine scans were carried out in each patient one to three days before surgery and two to nine days afterwards. All scans were reported by an experienced consultant radiologist, and the postoperative scans were closely scrutinized for any evidence of bleeding in the vertebral canal.

At the time of abstract submission, data from 20 patients in group 1 and 16 patients from group 2 were available. All patients in group 2 except two were taking aspirin 75–300 mg daily preoperatively. In group 1, the subarachnoid space was located on the first attempt in all except one patient who required two attempts, and no bleeding was seen during any of the procedures. In group 2, two attempts to locate the epidural space were necessary in two patients and mildly bloodstained fluid was aspirated initially from another two individuals. The blood stained aspirate rapidly cleared in these latter two patients and it was felt safe to continue with the block. There was no vertebral canal bleeding seen on MRI on these or any other of the postoperative scans.

MRI scanning can detect small haematomas but we have so far failed to find any bleeding following spinal or epidural block. It is particularly interesting that no bleeding was seen in the patients who had epidural catheters and had received aspirin preoperatively and heparin intraoperatively.

Acknowledgment

This work was supported by a grant from the Association of Anaesthetists of GB and Ireland.

Keywords: measurement techniques, magnetic resonance imaging; anaesthetic techniques, epidural

Reference

1. Tryba M. *Anästhesie Intensivmedizin Notfallmedizin Schmerztherapie* 1993; **28**: 179–181.

The influence of metoclopramide on the duration of action of mivacurium

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Mivacurium is metabolized by plasma cholinesterase (PCHE).[1] Metoclopramide inhibits PCHE in vitro and in vivo.[2] We aimed to assess the effect of metoclopramide on the duration of action of mivacurium.

Thirty ASA grade I or II patients scheduled for elective surgery were recruited. An initial blood sample was taken at insertion of a venous cannula (PCHE 1). Patients then received intravenous metoclopramide 0.15 mg kg^{-1} (n=15), or saline (n=15) in a double blind manner. Anaesthesia was induced with fentanyl 2 µg kg^{-1} and propofol 2.5 mg kg^{-1} and maintained by propofol infusion (6–10 mg kg^{-1} h^{-1}) and 66% nitrous oxide in oxygen. The lungs were ventilated to normocapnia and the forearm skin temperature kept above 32°C. Using a TOF Guard accelerometer (Biometer, Denmark) the ulnar nerve was stimulated in a train-of-four sequence at 15 s intervals, recording the first evoked response in the adductor pollicis (T1). After five minutes, mivacurium 0.15 mg kg^{-1} was given over five seconds into a free running infusion. The time to 95% suppression of T1 (onset time), times to recovery to 25% and 90% of baseline T1, and recovery index (25% T1 to 75% T1) were noted. A second venous blood sample was taken at maximum twitch suppression (PCHE 2). PCHE activity was determined spectrophotometrically by the rate of benzoylcholine hydrolysis at 25°C (µmol ml^{-1} min^{-1}).

Three patients heterozygous for atypical PCHE and one patient (saline group) in whom T1 only recovered to 78% of baseline T1 were excluded. The times to 25% and 90% recovery of T1 were prolonged in patients who received metoclopramide (table 5). PCHE activity within each group decreased ($P<0.01$) but there was no difference between the groups.

Mivacurium had a longer duration of action in patients who received metoclopramide. This effect was evident even though inhibition of PCHE by metoclopramide was not demonstrated.

Table 5 Onset and recovery times (min) and plasma cholinesterase (PCHE) activity. Values are mean (SD)

	Saline (n=12)	Metoclopramide (n=14)	P value (t test)
Onset time	3.2 (1.0)	2.6 (0.9)	0.11
T1 25%	13.4 (3.7)	17.8 (3.9)	<0.01
T1 90%	21.9 (6.2)	28.8 (8.1)	<0.05
Recovery index	5.8 (2.1)	7.5 (3.5)	0.15
PCHE 1	1.15 (0.25)	1.13 (0.21)	0.9
PCHE 2	1.0 (0.2)	0.99 (0.2)	0.9

Acknowledgement

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Keywords: neuromuscular block, mivacurium; pharmacology, metoclopramide; enzyme, cholinesterase

References

1. Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott RFP, Sunder N, Weakly JN, Wastila WB, Wl-Sayad HA. *Anesthesiology* 1988; **68**: 723–732.
2. Rao SS, Kaveeshwar U, Mishra PK. *Pharmazie* 1992; 47: 66–67.

Development of a self learning fuzzy controller for mivacurium induced neuromuscular block

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We have previously shown the value of self learning fuzzy logic for the control of neuromuscular blockade using atracurium.[1,2] We have now adapted the controller for use with mivacurium. Mivacurium has a markedly different pharmacokinetic/pharmacodynamic profile from atracurium and therefore presents a greater challenge to the fuzzy logic controller.

Ethics committee approval was obtained and 24 ASA 1, 2, or 3 patients gave written informed consent for inclusion in the study. After induction of anaesthesia with alfentanil 10 µg kg^{-1} and a sleep dose of propofol, a Datex Relaxograph was calibrated. This was interfaced to an HP 200LX palmtop computer and a Graseby Medical 3400 infusion pump to give mivacurium. A loading dose of mivacurium 0.25 mg kg^{-1} was given to facilitate tracheal intubation. Anaesthesia was maintained with a propofol infusion, nitrous oxide and oxygen, and morphine as appropriate. The setpoint for control was chosen as 10% of baseline twitch height. Fuzzy logic control of the infusion began when the T1 twitch height had returned to 5% of the baseline T1. Performance was assessed using T1 errors (actual T1 minus setpoint T1 value) during the period of neuromuscular control, using data logged by the computer. T1 errors were analysed for mean, standard deviation (SD), and root mean square deviation (RMSD). Mean mivacurium infusion rates for the period of control were also calculated for each patient.

The performance of the controller with the initial five patients was poor and alterations were made. A further nine patients were studied with some improvement. A third version of the programme was then written and used on the final 10 patients. The results of this version are presented in table 6.

Table 6 Summary of T1 error analysis and mivacurium infusion rate

		Mean	SD	Range
Error from set point (%)	Mean	−0.72	0.61	−1.85 to 0.47
	SD	2.51	0.97	1.26 to 3.83
	RMSD	2.96	1.02	1.57 to 4.12
Mivacurium infusion rate (mg kg^{-1} h^{-1})	Mean	0.38	0.13	0.27 to 0.69
	SD	0.06	0.03	0.04 to 0.12

We have shown that self learning fuzzy logic is appropriate for the control of mivacurium induced neuromuscular blockade, although good control was more difficult to achieve than with atracurium

Keywords: computer, fuzzy logic; neuromuscular block, mivacurium

References

1. Ross JJ, Mason DG, Linkens DA, Edwards ND. *British Journal of Anaesthesia* 1997; 78: 412–415.
2. Mason DG, Ross JJ, Edwards ND, Linkens DA, Reilly CS. *Medical and Biological Engineering and Computing* 1997; 35: 498–503.

Residual neuromuscular blockade from pancuronium after cardiac anaesthesia

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Many studies have shown a high incidence of postoperative residual neuromuscular blockade after anaesthesia involving long acting muscle relaxants such as pancuronium.[1] Residual neuromuscular blockade has been shown to increase the risk of postoperative pulmonary complications.[2] The importance of this problem has not been investigated in cardiac anaesthetic practice, where pancuronium retains a considerable popularity. The aim of this study was to investigate the prevalence of residual block caused by pancuronium in postoperative cardiac surgical patients at the time that they would normally be permitted to emerge from anaesthesia in the cardiac surgery unit (CSU).

We studied 18 adult patients who had undergone open heart surgery and cardiopulmonary bypass. During surgery all had received pancuronium as the sole muscle relaxant. The dose of pancuronium was left to the discretion of the anaesthetist. Postoperatively the patients were sedated with a continuous intravenous infusion of propofol, and their lungs were mechanically ventilated following routine practice in the CSU. From the time each patient arrived in the CSU, the train-of-four (TOF) ratio was measured at regular intervals using electromyography of the adductor pollicis and stimulation of the ulnar nerve at a frequency of 2 Hz and with a current of 80 mA (Disa Neuromatic 2000). Initially the nursing staff caring for the patient were kept unaware of the results of the measurements. If TOF was <0.8 at the time when they expressed their intention to stop the sedation, sedation and mechanical ventilation were continued at the request of the investigator. Once three consecutive measurements showing TOF$\geq$0.8 were obtained, the measurements were discontinued, sedation was stopped, and the patient's trachea was extubated as clinically appropriate.

Twelve of the 18 patients (95% confidence interval 41% to 87%) had a TOF of <0.8 at the time CSU staff wished to stop the sedation. At that point the median time after admission to CSU was 2 h (interquartile range 1 h 15 min to 3 h 17 min) and the mean TOF in these 12 patients was 0.36 (SE=0.075, range 0 to 0.7). Subsequently it took a median of 2 h 10 min (interquartile range 57 min to 2 h 50 min) to reach TOF $\geq$0.8. For all 18 patients the median time from admission to TOF $\geq$0.8 was 3 h 52 min (interquartile range 2 h to 5 h 1 min). The mean pancuronium dose was 0.12 mg kg^{-1} (SE=0.007, range 0.08 to 0.18 mg kg^{-1}).

These results show that in current cardiac anaesthetic practice commonly used doses of pancuronium leave a sizable proportion of patients partially paralysed at the time when they are allowed to regain consciousness in the CSU.

Keywords: neuromuscular block, pancuronium; surgery, cardiovascular

References

1. Viby-Mogensen J, Chraemmer-Jorgensen B, Ording H. *Anesthesiology* 1979; 50: 539–541.
2. Berg H, Viby-Mogensen J, Roed J, Mortensen C, Engbaek J, Skovgaard L, Krintel J. *Acta Anaesthesiologica Scandinavica* 1997; 41: 1095–1103.

Comparison of different dose regimens of remifentanil on the cardiovascular response to orotracheal intubation

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It is well documented that laryngoscopy and orotracheal intubation produce a transient rise in heart rate and blood pressure. Previously we have shown that remifentanil, 1 μg kg^{-1}, attenuates this response, but it may be associated with significant bradycardia and hypotension unless given with glycopyrrolate.[1] The aim of this study was to investigate in a randomized, double blind fashion the effect of a lower dose of remifentanil upon the cardiovascular response to intubation and the need for concurrent administration of glycopyrrolate.

Sixty ASA I–II gynaecological patients (aged 20–56 years) were randomized into three groups: (1) remifentanil 1 μg kg^{-1} bolus with 200 μg bolus of glycopyrrolate followed by infusion of 0.5 μg kg^{-1} min^{-1} infusion; (2) remifentanil 0.5 μg kg^{-1} bolus with 200 μg bolus of glycopyrrolate followed by a 0.25 μg kg^{-1} min^{-1} infusion; (3) remifentanil 0.5 μg kg^{-1} bolus with 1 ml saline bolus followed by a 0.25 μg kg^{-1} min^{-1} infusion.

Each patient received a standardized general anaesthetic consisting of the remifentanil regime, followed by a sleep dose of propofol, rocuronium (0.6 mg kg^{-1}), and ventilation with 67% N_2O in O_2 and 1% isoflurane. Laryngoscopy and intubation were performed three minutes after induction. Blood pressure was measured non-invasively by an automatic oscillometric device and pulse rate recorded from the pulse oximeter. Observations were recorded at 1 min intervals from before induction to 5 min after intubation. Data were analysed using ANOVA and unpaired *t* tests. Power analysis determined that 18 patients per group were needed to have greater than 80% power to detect a difference in mean arterial pressure of 10 mm Hg between the groups (using data from our previous study[1]).

The results are shown in table 7. Baseline heart rate was similar in all groups, but decreased in group 3 (saline) after induction of anaesthesia, and remained lower after intubation compared with the other groups ($P<0.05$). There were no differences in mean arterial pressure between the groups at any time points in the study. There were small increases in heart rate and mean arterial pressure after tracheal intubation, which were not clinically significant. The incidence of bradycardia or hypotension requiring escape medication was low (7/60), with no differences between the groups.

Keywords: analgesics opioid, remifentanil; intubation tracheal

Reference

1. Thompson JP, Hall AP, Russell J, Cagney B, Rowbotham DJ. *British Journal of Anaesthesia* 1998; 80: 467–469.

Table 7 Cardiovascular responses

	Preinduction, t=-3 min		Preintubation, t=0 min		Postintubation, t=1min		Postintubation, t=5 min	
	Mean (95% CI)		Mean (95% CI)		Mean (95% CI)		Mean (95% CI)	
Group	MAP	Pulse	MAP	Pulse	MAP	Pulse	MAP	Pulse
1	88 (4.5)	82 (5.9)	62 (4.9)	79 (6)	73 (7)	85 (7)	62 (3.5)	80 6.5)
2	91 (6.3)	85 (5.5)	59 (4.7)	81 (7)	75 (5.9)	90 (7.4)	61 (4.5)	78 (6.5)
3	88 (4.3)	77 (5.9)	60 (3.5)	69* (4.7)	71 (4.9)	57 (2.9)	63* (4.9)	

CI, ± value in brackets=confidence interval; MAP, mean arterial pressure (mm Hg); pulse, pulse rate (beat min^{-1}).
*$P<0.05$.

An updated two dimensional model for anatomical/blade interaction in tracheal intubation

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A three dimensional computer simulation of tracheal intubation is being developed with the aim of producing simulations based on patients' individual radiological imaging data. Preliminary stages have been reported.[1-4] The primitive two dimensional (2-D) anatomical/ blade interaction simulation[5] and individual magnetic resonance images (MRI) were used as the starting point for the three dimensional simulation. As physical properties were incorporated into tongue deformations it became clear that there was merit in continued parallel development of the original 2-D model for comparison.

The anatomical model described difficulty in terms of the restriction of forward movement of the laryngoscope blade relative to space available for the "residual volume of the tongue" (that part of the tongue not displaced to one side by the blade). Initial access to the oropharynx depends on blade shape and the degree of mouth opening (angles IJS and TIS) (fig 6). The eyeline is the tangent from where the laryngoscope flange touches the upper incisors to its pharyngeal surface. This depends on blade shape and depth of insertion into the pharynx. Blade shape and depth of insertion also influence forward blade rotation but this is mainly dependent on the tongue/space restriction (that is, how far forward the residual volume of the tongue limits forward rotation towards S). The tongue/space restriction is then modelled as a distance along SJ—that is, SM. This distance describes the maximum forward position for the lingual surface of the blade. As restrictive conditions worsen so the laryngoscope blade is effectively rotated backwards until no view of the larynx is feasible. Backwards rotation is eventually limited by the posterior pharyngeal wall and increasing difficulty then becomes a combination of still more backwards rotation but with progressive limitation for depth of blade insertion.

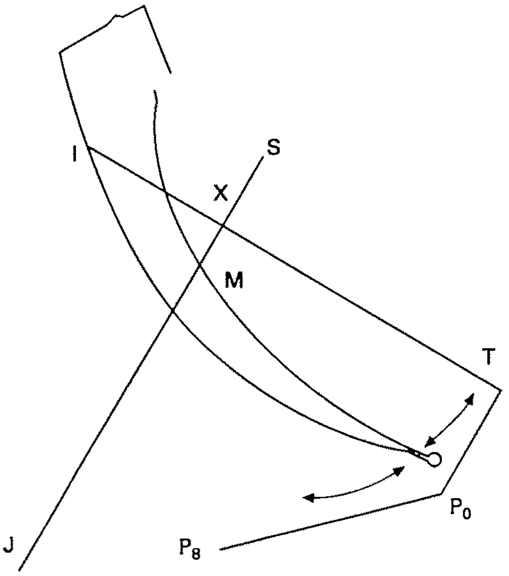

Figure 6 I, tip of upper incisors; T, anterior airway point at laryngeal inlet; J, midpoint between mandibular condyles; S, internal midpoint of ramus; X, intersection of JS and IT, P_0, posterior pharyngeal wall (arytenoid tip); P_8, posterior pharyngeal wall (at lower C2 body).

Simple measurements allow reconstruction of a patient's anatomical model. The limiting factor for this updated 2-D anatomical/blade interaction model is in accurately predicting SM. Degree of rotation of the blade about the incisors looks increasingly attractive as an objective measure of difficulty especially when combined with progressive limitiation for depth of insertion.

Keywords: intubation tracheal; model, mathematical

References

1. Charters P. *Canadian Journal of Anaesthesia* 1994; 41: 594–602.
2. Marks RRD, Hancock R, Charters P. *Canadian Journal of Anaesthesia* 1993; 40: 262–70.
3. Horton WA, Fahy L, Charters P. *British Journal of Anaesthesia* 1989; 62: 6–12.
4. Groom P, Charters P. *British Journal of Anaesthesia* 1997; 79: 680P–681P.
5. Marks RRD, Hancock R, Charters P. *British Journal of Anaesthesia* 1992; 68: 439P–440P.

Capnography during ventilation in intensive care

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During pressure controlled ventilation (PCV) in lung disease, a given inflation pressure level is combined with other ventilatory settings to obtain adequate CO$_2$ removal. If "optimal" CO$_2$ removal could be defined, this might aid optimal ventilator adjustment. Such conditions could include those giving: (1) maximum CO$_2$ clearance; (2) maximum CO$_2$ clearance per unit ventilation (that is, lowest dead space ratio); or (3) maximum CO$_2$ clearance per unit mean or peak airway pressure. We have used the Siemens 930 capnograph,[1] which measures not only end tidal CO$_2$ (Pe'CO$_2$) but also the minute elimination of CO$_2$, $\dot{V}$co$_2$. This allows rapid assessment of the effect of any change in ventilator setting on CO$_2$ elimination, as any increase in $\dot{V}$co$_2$ is proof of increased alveolar ventilation when metabolism is constant.[2]

Permission to perform the studies was obtained from relatives of six intensive care patients undergoing PCV with a Servo 900C ventilator. All patients were cardiovascularly stable and none had a Pao$_2$ of less than 9.0 kPa. Fio$_2$ was 0.30 to 0.75. Median positive end expiratory pressure (PEEP) was 10 cm H$_2$O, and median Ppeak 29 cm H$_2$O. After baseline observations at the patient's original ventilator setting, all ventilatory and gas exchange variables were noted and blood gases taken. Ventilator rate was then changed randomly, in steps of multiples of 3 min^{-1}, between 9 and 30 min^{-1}, with other variables unchanged. New readings were taken after two minutes; $\dot{V}$co$_2$ was also noted at 30 and 60 seconds. The rate was then returned to baseline for two minutes. After new readings, another rate was chosen and the sequence repeated. At the setting which gave the greatest $\dot{V}$co$_2$, blood gases were taken after 20 minutes. Thereafter inspiratory: expiratory (I:E) ratio was varied between 1:3, 1:2, 1:1, and 2:1.

We investigated 18 to 39 settings in each of six patients. In each patient maximum $\dot{V}$co$_2$ was obtained at a greater ventilatory rate than baseline. The maximum $\dot{V}$co$_2$ (at 120 s) that could be obtained by adjusting the ventilator ("best" setting) was greater than baseline $\dot{V}$co$_2$; the mean increase was 5% (95% confidence interval 0.7% to 9.6%). The mean "best" $\dot{V}$co$_2$, per unit mean airway pressure, exceeded baseline by 11% (5% to 15%). Median V_D/V_T at baseline was 0.44, while at "best" setting it was 0.51 ($P<0.05$). Median tidal volume was 0.70 litre at baseline and 0.59 litre at best setting ($P<0.05$). Pao$_2$ and Sao$_2$ were unchanged at the optimum setting because end expiratory pressure varied little. At the baseline I:E ratio, a peak or plateau value for $\dot{V}$co$_2$ was evident at greater rate settings, and in five patients this was at more than 20 min^{-1}. If changing setting increased $\dot{V}$co$_2$, the median value after 30 s at the new setting was 100.4% (100.1% to 101.1%) of that at two minutes (n=80) If the change reduced $\dot{V}$co$_2$, after 30 s it was 100% (99.2% to 101.1%) of the value at two minutes (n=89).

This study shows that CO$_2$ eliminaton can be assessed within 30 seconds of changing ventilator setting. Traditional low ventilator rates, with the lowest V_D/V_T, do not clear most CO$_2$. With high airway pressures, $\dot{V}$co$_2$ per unit mean or peak airway pressure, the measurement of which may minimize barotrauma, may be a more relevant ventilatory index than V_D/V_T. This method allows rapid "trawling" to find a rational ventilator setting.

Keywords: ventilation, carbon dioxide; airway, pressure

References

1. Olsson SG, Fletcher R, Jonson B, Prakash O. *British Journal of Anaesthesia* 1980; 52: 491–498.
2. Taskar V, John J, Larsson A, Wetterberg T, Jonson B. *Chest* 1995; 108: 196–202.

Comparison of plasma and urinary pro- and anti-inflammatory cytokine changes during cardiac surgery

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Maintenance of pro- and anti-inflammatory cytokine homeostasis in plasma and in the respiratory and gastrointestinal tracts has been shown to be important in a variety of inflammatory diseases.[1] Cardiac surgery involving cardiopulmonary bypass (CPB) invokes changes in this homeostasis within both the plasma and the organ systems.[2] In this study we investigated the relation between plasma and urinary cytokine homeostasis in patients undergoing coronary artery bypass grafting (CABG).

Twenty patients undergoing elective CABG were anaesthetized with fentanyl 20–25 μg kg^{-1}, pancuronium 100–150 μg kg^{-1}, propofol (target concentration 0.5–4.0 μg ml^{-1}) and further increments of fentanyl. Baseline (sample 0) plasma and urine samples were obtained before and immediately after induction of anaesthesia, respectively. Further samples were obtained after cross clamp release (sample 1), and 2 and 24 h post-CPB (samples 2 and 3). The samples were analysed by ELISA using commercially available cytokine kits (Quantikine, R&D Systems Europe). The pro-inflammatory cytokines tumour necrosis factor α (TNFα) and interleukin-1β (IL-1β) and the anti-inflammatory cytokines TNF soluble receptor 2 (TNFsr-2) and interleukin-1 receptor antagonist (IL-1ra) were assayed. Aprotinin was not included. Within group results were analysed by Friedman's analysis of variance with Dunn post test as appropriate.

IL-1β was not detected in urine or plasma at any time. TNFα was not detected in urine but was detected in plasma in only samples 1 and 2 at concentrations of 11.1 (36.6) and 9.7 (15.2) pg ml^{-1} (mean (SD)) respectively. IL-1ra and TNFsr-2 were significantly increased in both plasma and urine when compared with baseline (table 8). The increases in TNFsr-2 and IL-1ra in urine were greater than the increases in plasma and may be a useful alternative indicator of cytokine balance.

Acknowledgement

We would like to thank the Association of Anaesthetists of Great Britain and Ireland for financial support.

Keywords: heart, cardiopulmonary bypass; immune response; polypeptides, cytokines

References

1. McBride WT, McBride SJ. *Current Opinion in Anesthesiology* 1998; 11: 15–22.
2. McBride WT, Armstrong MA, Crockard AD, McMurray TJ, Rea JM. *British Journal of Anaesthesia* 1995; 75: 724–733.

Use of a microdialysis system under hyperbaric conditions

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Microdialysis is a technique for collecting interstitial substances in vivo, with minimal tissue disruption.[1] It is based on the transfer of substances down a concentration gradient across a dialysis membrane inserted into the tissue. Equipment produced by CMA/Microdialysis AB is CE labelled with probes for use in human adipose tissue and skeletal muscle. The pump had been modified to include a small hole in the casing. The probes connect to a syringe of dialysate at one end and a collecting vial at the other. A major concern in microdialysis is that of recovery—that is, how well the concentration of a substance in the collected fluid reflects its interstitial concentration. Recovery is affected by dialysate flow rate, decreasing as flow increases.[2] The CMA system uses a flow of 0.3 μl min^{-1} through dialysis catheters of 30 mm to achieve recoveries around 100%. We wished to use the system in a hyperbaric chamber but its function at high pressure was not known. If flow increased markedly, recovery would decrease making interpretation of results difficult. With reduced flow, one would need to collect for long periods to obtain sufficient volume for laboratory analysis. We considered a flow between 0.2 and 0.4 μl min^{-1} would be desirable to ensure suitable collection volumes and optimum recovery. This bench test was carried out to check functioning of the system before performing any work in humans.

The weight of 10 collecting vials was recorded. Deionized water was pumped through the probe using a CMA 106 pump and collected for 30 minutes into each vial, which were then weighed again; 9 μl water should be collected, which would weigh 0.009 g. The experiment was repeated after the pump had been subjected to 6 atmospheres absolute pressure (ATA), and then conducted twice in the hyperbaric chamber at 4 ATA using five vials.

The results are shown in table 9. An unexplained decrease in flow (vial 10, first run) improved subsequently. This also occurred in the post-50m test (vials 6 and 7) but not when tested at pressure. On no occasion did we observe any marked increase in flow that might adversely affect recovery.

Acknowledgement

We wish to thank the staff of NWERU for their cooperation and help with this study.

Keywords: equipment, microdialysis

References

1. Delgado JMR, DeFeudis FV, Roth RH, Ryugo DK, Mitruka BM. *Archives Internationales de Pharmacodynamie et de Therapie* 1972; 198: 9–21.
2. Benveniste H, Hüttenmeier PC. *Progress in Neurobiology* 1990; 35: 195–215.

Table 8 Mean (SD) TNFsr-2 and IL-1ra values

		Sample 0	Sample 1	Sample 2	Sample 3
TNFsr-2 (pg ml^{-1})	Plasma	1286 (1052)	1358 (2139)	2077 (2761)**	2471 (3441)**
	Urine	1946 (1187)	12257 (7711)**	12009 (7117)**	14858 (7128)**
IL-1ra (pg ml^{-1})	Plasma	229 (128)	527 (199)*	4597 (2340)**	1580 (1150)**
	Urine	841 (814)	4507 (2950)**	15325 (9373)**	11774 (8573)**

*$P<0.05$; **$P<0.01$ *v* baseline.

Table 9 Flow (μl min^{-1}) into each vial

	1	2	3	4	5	6	7	8	9	10	11	12	13
1st run	0.35	0.31	0.32	0.31	0.32	0.30	0.27	0.28	0.26	0.09	0.11	0.25	0.29
Post 50 m	0.24	0.27	0.22	0.22	0.18	0.02	0.06	0.17	0.19	0.24	—	—	—
At 30 m (1)	0.26	0.23	0.21	0.22	0.21	—	—	—	—	—	—	—	—
At 30 m (2)	0.37	0.30	0.28	0.28	0.30	—	—	—	—	—	—	—	—

Extravascular lung water and ARDS – oxygenation and outcome

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Adult respiratory distress syndrome (ARDS) comprises a constellation of pathophysiological events culminating in lung compliance, capillary permeability, and gas exchange defects. Non-cardiogenic interstitial and alveolar oedema are thought to be major determinants of the clinical lesion. We have therefore studied the influence of extravascular lung water (EVLW) on oxygenation and outcome.

We studied 11 consecutive ARDS patients with a Pao_2/Fio_2 ratio (mm Hg) of <150, bilateral infiltrates on chest *x* ray, and pulmonary artery occlusion pressure less than 18 mm Hg. All patients were mechanically ventilated using a standardized ventilatory protocol. Inspired oxygen concentration was adjusted to an initial target Pao_2 of greater than 8.0 kPa. All patients received inhaled nitric oxide (NO) at a concentration of 20 vol million^{-1}. Central venous and pulmonary artery pressures were measured. A 3F combined fibreoptic–thermistor catheter was introduced into the proximal abdominal aorta and connected to an integrated fibreoptic monitoring system (COLD Z-021, Pulsion, Munich, Germany). Extravascular lung water measurements were made by a dual indicator technique. Patients were managed with fluids and inotropes according to a standard protocol. Results are expressed as median (range) or mean (SEM) as appropriate.

Median age was 45 (27 to 60) years. Overall admission APACHE score was 31 (17 to 36). The overall duration of mechanical ventilation was 15 (6 to 28) days. Murray lung injury score, oxygenation data, and extravascular lung water index (EVLWI) on admission are tabulated.

The results are shown in table 10. The only variables independently predictive of Pao_2/Fio_2 ratio were positive end expiratory pressure (PEEP) (B=6.82 (1.94)) and EVLWI (B=–2.18 (0.45)), r^2=0.37, P<0.0001. In severe ARDS (Pao_2/Fio_2 <150 mm Hg) EVLWI was 24.4 (1.03) ml kg^{-1} compared with 15.1 (1.5) ml kg^{-1} during moderate ARDS (P<0.001). Serum albumin also differed, at 29.4 (0.9) *v* 35.1 (1.7) g l^{-1}, P<0.005. PAOP was higher during periods of poor oxygenation, at 12.7 (0.4) *v* 9.3 (0.7) mm Hg, P<0.001. There were four survivors. Ages of survivors (50.5 (38 to 60) years) and non-survivors (39 (27 to 57) years) did not differ (P=0.26). Murray score was similar in survivors, 2.8 (2 to 3), and non-survivors, 2.6 (2 to 3), P=0.6. APACHE score was 27.5 (17 to 33) in the survivors and 33 (24 to 36) in the non-survivors (P=0.18). Survivors had greater initial EVLWI than non-survivors, 31 (3.5) *v* 20.7 (2.4) ml kg^{-1}, P=0.034, and went on to show a greater reduction in lung water than non-survivors, at 15.2 (3.0) *v* 5.4 (1.7) ml kg^{-1}, P=0.013. Duration of mechanical ventilation was greater in survivors, at 21.5 (15 to 23) days *v* 9 (6 to 28) days in those who died (P=0.088).

Table 10 Measured variables

	Median	Minimum	Maximum
Albumin (g l^{-1})	30	20	47
Creatinine (mmol l^{-1})	145	46	312
EVLWI (ml kg^{-1})	20.8	8.7.	54.7
Murray score	2.5	2	3
Pao_2/Fio_2 ratio (mm Hg)	110.5	45.7	195

EVLWI, extravascular lung water.

Extravascular lung water is a marker of the severity of ARDS. Further work is required to assess the role of EVLWI manipulation on clinical outcome.

Keywords: lung, adult respiratory distress syndrome

POSTER PRESENTATIONS

"On line" monitoring of cerebral evoked responses

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During experiments to investigate the effects of anaesthetic agents it is often necessary to know whether the animal preparation is in a stable condition or whether the effect of an anaesthetic under study has (a) reached a plateau effect or (b) worn off. One very sensitive indicator of anaesthetic effect is the latency of the averaged cerebral response evoked by a peripheral stimulus. This latency can be measured in one of two ways. If the baseline of the response is electrically clean the regression line of the baseline can be determined (fig 7A, R) and the latency estimated by determining when the response deviates from the regression line by a fixed amount (fig 7A, L+). In this case it is then easy to measure the first positive wave of the cortical response (fig 7A, P) and the first negative wave (fig 7A, N). If the baseline is not electrically clean the latency change between responses can be determined using a different approach. For this the peak of the first positive wave is detected using an algorithm based on wavelet theory.[1] The best slope of the line leading to this peak is then determined using an iterative regression determination in a control average. In subsequent responses the average time difference between the slopes of the current response and the control response will give the latency change between these responses (fig 7B). Both methods have been programmed to allow their use "on line" during an experiment and also "off line" for data measurement, thus allowing stored sequential long time period recordings of averaged evoked responses to be analysed easily. Comparison of manual data analysis and the automatic analysis shows that both methods are robust.

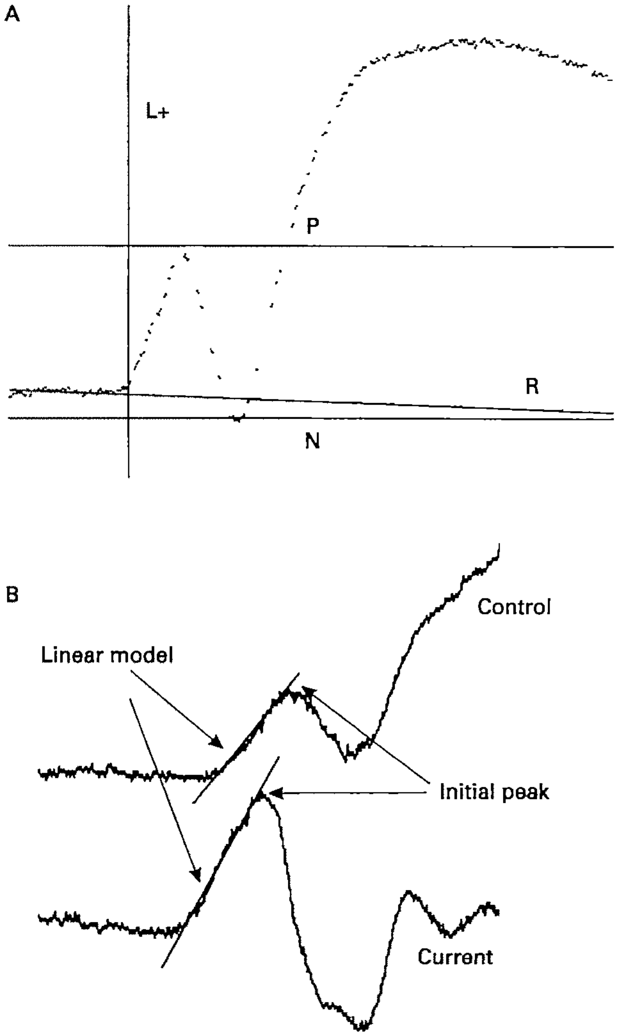

Figure 7 Methods used to estimate the latencies of cerebral averaged evoked responses and to determine the amplitudes of the initial positive and negative waves of the responses.

Acknowledgement

CHT was supported by a postgraduate scholarship from the University of Sheffield.

Keywords: brain, evoked potentials

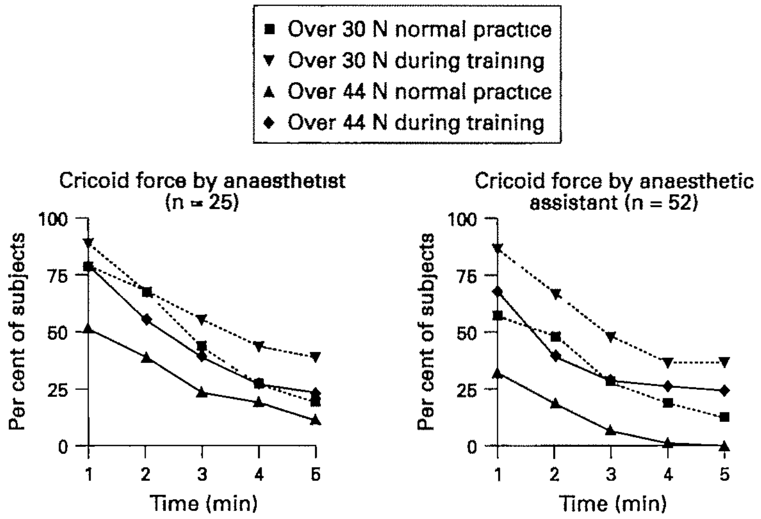

Figure 8 Comparison of anaesthetists and anaesthetic assistants.

Reference

1. Daubechies I. *Communications on Pure Applied Mathematics* 1988; 41: 1104–1135.

Can cricoid force be maintained for five minutes?

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The use of cricoid force was described by Sellick.[1] Standard teaching is to maintain a force of 44 N until the airway is secured, although 30 N has been shown to be sufficient in cadavers.[2] The aim of this study was to determine if anaesthetists and anaesthetic assistants can maintain a force of 44 N on a simulated cricoid cartilage over a five minute period. We examined the force applied in their normal practice and then ability to maintain a cricoid force using visual feedback on a computer screen.

All studies were performed on a bench model of cricoid cartilage made from plastic (PTFE) which was fixed to a load cell (0–20 kg). The load cell was connected to an amplifier and a computer. The applied force was recorded every second for a 5 min period. The force applied was displayed on a computer screen, which could be seen by the subject in the second part of the study. Each subject was assessed twice: (1) to apply cricoid force which they use in normal practice and maintain it for five minutes, (2) to apply cricoid force and maintain it for five minutes by observing a computer reading of force applied.

In their normal practice none of the anaesthetic assistants and only 12% of the anaesthetists maintained a force of 44 N for five minutes (fig 8). With the force displayed to the subject this improved to 25% of anaesthetic assistants and 24% for the anaesthetists. In their normal practice 13% of anaesthetic assistants and 20% of anaesthetists maintained a force of 30 N for five minutes. With the force displayed this improved to 37% for anaesthetic assistants and 40% for anaesthetists.

The cricoid force used in normal practice by both the anaesthetists and anaesthetic assistants in our study falls well below that recommended. It improved when subjects were aware of the amount of force required but most subjects were unable to maintain a force of even 30 N for five minutes.

Acknowledgement

We wish to thank Professor D. Rowbotham and Dr P. Spiers for their support.

Keywords: larynx, cricoid pressure; anaesthetists, training

References

1. Sellick BA. *Lancet* 1961; ii: 404–406.
2. Vermer RG, Pryle BJ. *Anaesthesia* 1992; 47: 732–735.

Effect of steroidal neuromuscular blocking drugs on norepinephrine uptake in SH-SY5Y cells

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The causes of cardiovascular side effects associated with the use of steroidal neuromuscular blocking drugs (NMBD) are unclear. Pancuronium and rocuronium may be associated with tachycardia[1 2] and vecuronium with bradycardia.[3] Previous work has shown that NMBD interact with m2 muscarinic receptors at clinically relevant doses.[4] Sympathetic stimulation leads to norepinephrine release and this affects the heart. Norepinephrine reuptake in isolated rat hearts is inhibited by steroidal neuromuscular relaxants.[5] In this study we have examined the effects of four NMBDs on norepinephrine uptake in SH-SY5Y neuroblastoma cells as a model of human sympathetic neurones.

All studies were performed in 0.5 ml of Krebs/HEPES buffer, pH 7.4, using a modification of the method described by Atcheson *et al.*[6] Whole cells were incubated in the presence of NMBD (10^{-8}–10^{-4}) for 30 min. The reaction was started by addition of ~41 nM [^{3}H]-norepinephrine and incubated for a further 5 min. The reaction was terminated by vacuum filtration on a Brandell cell harvester. Non-specific uptake was determined in the presence of 200 μM imipramine. [^{3}H]-Norepinephrine uptake was time dependent and inhibited by imipramine with a pIC$_{50}$ of 7.15 (0.06) (mean (SEM)) (fig 9). Pancuronium, vecuronium, and rocuronium inhibited uptake but a pIC$_{50}$ value could not be calculated.

The inhibition of [^{3}H]-norepinephrine uptake did not occur at clinically relevant doses and as such norepinephrine uptake is unlikely to explain the cardiac side effects of these agents.

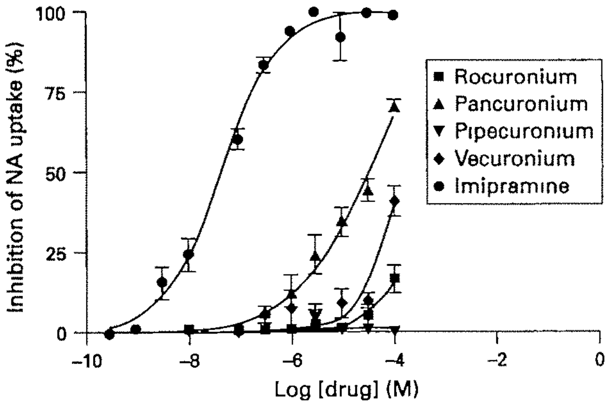

Figure 9 Inhibition of norepinephrine (NA) uptake by steroidal neuromuscular blocking drugs and imipramine. Values are means, error bars=SEM (*n*=7 except for imipramine, where *n*=4).

Table 11 Duration of action and recovery following cisatracurium 0.1 mg kg^{-1}

	Children				Adults				
	Mean	SD	Min	Max	Mean	SD	Min	Max	*P* value
T1=25% (min)	29.9	9.2	15	44	34.8	6.9	20	45	0.1826
T1=90% (min)	47.9	12.5	29	67	54.2	9.4	38	71	0.1916
T1 25–75% (min)	13.5	3.3	9	18	14.0	4.0	8	21	0.7384
T4/T1=0.8 (min)	53.3	8.5	40	70	63.0	7.5	48	74	0.0050
T1=25 to T4/T1=0.8 (min)	23.3	5.2	16	32	28.2	4.5	22	37	0.0209

Acknowledgment

Vecuronium and rocuronium were donated by Organon Teknika. TMC holds a University of Leicester PhD studentship.

Keywords: neuromuscular block; sympathetic nervous system, norepinephrine

References

1. Leeson S, Waud BE, Waud DR. *Anesthesiology* 1981; 55: 12–18.
2. Mellinghoff H, Diefenbach C, Buzello W *Anesthesiology* 1991, 75: A807.
3. Stevens JB, Hecker RB, Talbot JC, Walker SC. *Acta Anesthesiologica Scandinavica* 1997; 41: 502–505.
4. Sherwin JD, Cembala TM, Appadu BL, Lambert DG. *British Journal of Anaesthesia* (in press).
5. Salt PJ, Barnes PK, Conway CM. *British Journal of Anaesthesia* 1980; 52: 313–317.
6. Atcheson R, Rowbotham DJ, Lambert DG. *British Journal of Anaesthesia* 1993; 71: 540–543.

Pharmacodynamics of cisatracurium in children and adults: a comparative study

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To date, dose–response data for cisatracurium in children during opioid anaesthesia have not been reported. The aim of this study was thus to provide such information while directly comparing the pharmacodynamics of cisatracurium in children and adults undergoing the same surgical procedure.

After approval by the local ethics committee, 15 children (2–12 years) and 15 adults, ASA class I and II, undergoing elective cochlear implant surgery were included with their or their parents' informed consent. Oral midazolam 0.3–0.5 mg kg^{-1} up to a maximum of 10 mg was given as premedication. Anaesthesia was induced with methohexital 1–4 mg kg^{-1} and remifentanil 0.5–1 g kg^{-1} min^{-1} and maintained by continuous infusion of these agents and ventilation with N_2O/O_2. Neuromuscular transmission was monitored using train-of-four stimulation at 20 s intervals (Datex Relaxograph®) after anaesthesia was stabilized, using calibrated monitors. For determination of the dose–response relationship, patients were randomly allocated to receive an initial cisatracurium dose of 0.02, 0.03, or 0.04 mg kg^{-1}. Maximum block was recorded. At the time of maximum block following the initial dose, a supplementary dose of cisatracurium was given (0.08, 0.07, or 0.06 mg kg^{-1}, respectively) such that all patients received a total dose of 0.1 mg kg^{-1}. Duration and recovery data following the supplementary dose were compared using the Mann–Whitney rank sum test. $P \leq 0.05$ was considered significant.

Data on duration of action and recovery are shown in table 11. ED50 and ED95 were 0.0376 mg kg^{-1} and 0.0568 mg kg^{-1} in children and 0.0333 mg kg^{-1} and 0.0527 mg kg^{-1} in adults, respectively.

Dose–response profile, clinical duration of action, and recovery of T1 height did not vary between children and adults. Train-of-four recovery was significantly faster in children. While it may be interesting to reflect on the underlying mechanisms of these differences, their clinical relevance is doubtful.

Keywords: neuromuscular block, cisatracurium; pharmacodynamics

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Proceedings of the Intensive Care Society and Riverside Group "State of the Art" Meeting

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(The name of the presenting author is shown in bold type.)

Agreement between ante-mortem clinical diagnosis, death certificate and post-mortem causes of death in critically ill patients

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Our aims were: (i) to determine agreement between ante-mortem clinical diagnosis, death certificate and post-mortem causes of death; (ii) to compare post-mortem rates on the intensive care unit with the national recommendations; and (iii) to determine the incidence of unexpected findings.

The disease or condition leading directly to death (Ia on the death certificate and post-mortem report) was compared with the ante-mortem clinical diagnosis. The level of agreement between the ante-mortem cause of death, death certificate and post-mortem report was assessed. Unexpected post-mortem findings were noted and their probable impact on the patient's outcome estimated.

The post-mortem rate in our unit was 35%. Agreement between the ante-mortem clinical diagnosis and post-mortem diagnosis was higher (58%) than when the death certificate was compared with the post-mortem diagnosis (40%). Discrepancies between the ante-mortem clinical diagnosis and death certificate were found in 32% of cases. Unexpected findings were found in 42%, of which 9% could have influenced the patient's final outcome. The commonest significant unexpected findings were misdiagnosis of myocardial infarction and pulmonary embolism.

The study suggests that although the incidence of clinically important unexpected findings was low, post-mortem examination offers the opportunity to amend the death certificates which we found did not agree with the clinical ante-mortem diagnosis in almost one-third of deaths.

Keywords: intensive care; intensive care, audit; complications, mortality

Changes in nocturnal oxygen saturation and ventilatory patterns in patients who have undergone prolonged mechanical ventilation

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There is a significant incidence of sleep-related breathing disorders after general anaesthesia with both obstructive and central apnoeas reported. We hypothesized that patients who underwent prolonged mechanical ventilation for critical illnesses would also have significant sleep-related disturbances in respiration.

We performed a pilot study in eight consecutive patients discharged from the intensive care unit who received more than 72 h of mechanical ventilation. Patients with a past history of chronic respiratory disease were excluded. Overnight multi-channel polysomnography was performed within 72 h of discharge using a Densa DMS500 system. Oxygen saturation, airflow, chest and abdominal wall movement, and snoring were recorded continuously, and apnoeas, hypopnoeas and length of periods of desaturation calculated. All patients received continuous oxygen overnight during the studies.

We studied eight patients (three males), median age 69 (range 54–77) yr, with a median duration of ventilation of 17 (range 3–49) days (table 1). Seven patients had episodes of nocturnal hypoxaemia often associated with abnormal respiratory patterns, despite oxygen therapy. The apnoea/hypopnoea index was abnormal in seven patients (predominately obstructive in two and predominately hypopnoeas in five) suggesting that sleep-related breathing disorders may be common after prolonged mechanical ventilation.

Table 1 Incidence of nocturnal hypoxaemia and oxygen saturation values in the eight patients studied

Patient No.	Apnoea index h^{-1}	Minimum Sa_{O_2} (%)	Time (%) in apnoea/hyponea	Time (%) Sa_{O_2} <90%
1	34	74	41	7
2	20	74	16	44
3	18	74	21	11
4	15	79	11	39
5	11	59	6	36
6	9	90	9	0
7	5	80	6	43
8	0	80	0	5

Keywords: sleep apnoea; oxygen, saturation; ventilation, apnoea

Use of pre-sedation GCS improves the performance of APACHE III when the GCS cannot be assessed

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The GCS is an important component of the APACHE III score When the GCS cannot be assessed because of sedation, APACHE assumes that the score is 15. The objective of this study was to examine the effect of using a pre-sedation GCS in this situation (as is done in SAPS) on the performance of APACHE III.

The APACHE III score, predicted and actual hospital mortality, were recorded for 10 326 patients admitted to 22 Scottish intensive care units during 1995–1996. When the GCS could not be assessed because of sedation, it was assigned a normal value. Scorers also recorded the pre-sedation GCS for these patients. The APACHE III score and mortality prediction were then recalculated using these values, producing an alternative database. Calibration and discrimination of the two databases were compared using the Hosmer–Lemeshow statistic and area under the ROC curve, respectively.

The GCS was assessed in 5202 patients but 5124 were recorded as being sedated. When the GCS of the sedated patients was assumed to be normal, APACHE III demonstrated good discrimination but relatively poor calibration. When the pre-sedation GCS was used, both discrimination (P<0.001) and calibration improved. When patients who were sedated or had a neurological diagnosis were analysed separately, similar improvements were seen (table 2).

Table 2 APACHE III (APIII) score and alternative database. Calibration and discrimination of the two databases were compared using the Hosmer–Lemeshow statistic and area under the ROC curve, respectively, for all patients, those sedated and those with a neurological diagnosis

	Area under ROC curve			Hosmer–Lemeshow chi-square		
	All patients	Sedated	Neurological	All patients	Sedated	Neurological
APIII	0.8446	0.8098	0.8568	331.65	484.24	76.41
Alternative	0.8519	0.8156	0.8753	126.89	148.44	13.96

When it is not possible to record the GCS in an ICU patient it may be preferable to use a pre-sedation value rather than assume that the GCS is normal.

Keywords: intensive care; anaesthesia, neurosurgical

Tracheal gas insufflation: performance of a phase-specific device and quantification of changes in functional residual capacity in pigs

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Pressure and volume limitation may lessen ventilator-induced lung injury, and hypercapnia is tolerated. An adjunctive method to limit this is end-expiratory washout (EWO), flushing carbon dioxide from the area proximal to the carina at end-expiration. Problems include tracheal damage, increased functional residual capacity (FRC) and potential barotrauma. We have evaluated a prototype EWO system with novel features.

The lungs of four anaesthetized Large-White pigs were ventilated via a 8.0-mm internal diameter tracheal tube using a pressure-controlled mode at 12 bpm. A catheter delivered EWO gas to a point 1 cm above the carina. Maximum and minimum tracheal pressures were measured (P_{trach}max and P_{trach}min). The study was performed in two phases. The first quantified the decrease in Pa_{CO_2} obtained using EWO while not allowing P_{trach}max to increase. The second quantified the reduction in tidal volume allowed by EWO at isocarbia. Data were compared using the paired *t* test, with $P<0.05$ considered significant.

Mean weight was 49 (SD 5.8) kg. Carbon dioxide production and temperature were stable throughout. In phase 1, mean Pa_{CO_2} during EWO was lower than before EWO (8.28 *vs* 9.61 kPa; $P<0.05$), by 13.9%. This occurred despite the P_{trach}max and P_{trach}min difference (ΔP_{trach}) decreasing from 7.5 to 6.3 cm H_2O as pressure-controlled mode held P_{trach}max constant. This was caused by an increase in P_{trach}min from 2.2 to 3.58 cm H_2O causing an associated decrease in V_T, from 236 (53) to 199 (41) ml, and an increase in FRC of 72 (8.8) ml.

In phase II, mean Pa_{CO_2} was held constant throughout (9.17 *vs* 9.35 kPa; ns). EWO allowed a reduction in expired tidal volume from 233 to 162 ml ($P<0.001$), a decrease of 39.8%. ΔP_{trach} also decreased during this phase (6.6 *vs* 5.2 cm H_2O; $P<0.05$), mainly as a result of a mean increase in P_{trach}min from 2.0 to 4.7 cm H_2O ($P<0.05$) as mean P_{trach}max decreased only slightly. FRC increased by 75.3 (25) ml.

We conclude that EWO reduced Pa_{CO_2} at constant peak tracheal pressure or allowed reduction in inflation pressure at isocarbia. Pressure-controlled modes are advisable because of small increases in FRC. However, reduced lung compliance of any patient receiving EWO should lessen this.

Keywords. lung, injury; lung, functional residual capacity; carbon dioxide, partial pressure; pig

Nitric oxide synthase inhibition prevents endotoxin impairing hepatocyte mitochondrial function

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We have reported previously that endotoxin (LPS) reduces the maximal capacity of Hep G2 cells to consume oxygen. This was in non-hypoxic cells, suggesting that at least some of the apparent anaerobic respiration seen in sepsis is related to a mitochondrial rather than a circulatory defect.

Oxygen consumption rate (OCR) was calculated from the rate of fall of Po_2 in a sealed vessel containing a Hep G2 cell suspension. Introduction of a mitochondrial uncoupler (FCCP) during the fall in Po_2 allowed baseline and maximal OCR to be calculated from the same cell sample. Four groups were studied ($n=12$): control group (group C); cells were exposed to L-NAME 1 µmol litre^{-1} (group Ln), LPS 10 µg ml^{-1} (group E) or L-NAME 1 µmol litre^{-1} with LPS 10 µg ml^{-1} (group Ln-E). In addition, media from groups C and E were tested for nitrite and nitrate concentrations using a standard colorimetric method. Statistical analysis was by factorial ANOVA (Fisher's *post hoc*).

OCR results are shown in figure 1. There was no significant difference in nitrite and nitrate concentrations between group C (2.8 (SD 0.25) µmol) and group E (4.5 (1.0) µmol) ($P=0.054$).

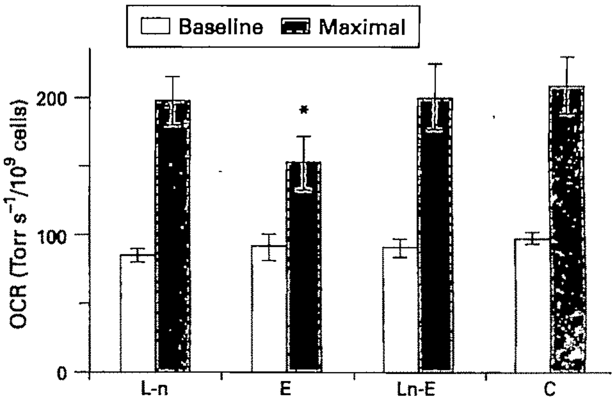

Figure 1 Maximal and baseline oxygen consumption rate (OCR) in the four groups. *$P<0.05$ *vs* control.

These data support our previous work showing impairment of energy metabolism in hepatocytes exposed to LPS. Prevention of impairment of maximal OCR by L-NAME despite lack of a detectable difference in nitrite and nitrate concentrations between groups C and E suggests: (i) the nitric oxide effect is mediated by very low concentrations acting locally; (ii) nitric oxide production has ceased by 24 h but has a lasting defect; or (iii) L-NAME has other unknown effects. The current state of knowledge suggests that (i) is the more likely.

Keywords: oxygen, consumption; pharmacology, nitric oxide; metabolism, oxygen consumption

Hypoadrenalism in children with septic shock

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We have investigated the incidence and effects of adrenal insufficiency (AI) in paediatric septic shock.

We studied children admitted to the PICU from May 1996 to April 1997 with septic shock. On admission, a short Synacthen test was performed (dose 145 µg m^{-2}). Adrenal failure was defined as baseline cortisol <100 nmol litre^{-1}. AI was defined *a priori* as a maximum post-synacthen increment of <200 nmol litre^{-1} (non-responder group). Data were analysed using the Mann–Whitney test, Fisher's exact test and chi-square test for trend.

We studied 33 children (33% mortality (n=11)) with a median age of 48 (range 1–192) months and median PRISM 17 (4–36). AI was present in 17 patients (52%). One patient had adrenal failure. Non-responders were more likely to require epinephrine for haemodynamic support (P=0.032; odds ratio 6.2; confidence interval 1.27–30 19) and also required higher dose vasopressors than responders, using either the paediatric inotrope score (P=0.0038; chi-square test for trend) or the sepsis-related organ failure assessment score (P=0.023) (table 3).

Table 3 Median (range) PRISM, cortisol concentrations and mortality rate in the 33 children with (non-responders) or without (responders) adrenal insufficiency

Variable	Non-responders (n=17) (52%)	Responders (n=16) (48%)	P
PRISM	18 (9–36)	12 (4–26)	0.06
Baseline cortisol	1018 (30–3264)	1083 (637–4553)	0.66
Mortality (n (%))	6 (35%)	5 (31%)	1.0

We conclude that adrenal insufficiency occurred frequently in children with septic shock and was associated with increased vasopressor requirements, but not with increased mortality.

Keywords: complications, hypoadrenalism; intensive care; complications, septic shock

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Effects of the selective inducible nitric oxide synthase inhibitor L-NIL on circulatory failure and multiple organ injury caused by endotoxaemia in the rat

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We have investigated if the highly selective inducible nitric oxide synthase (iNOS) inhibitor L-N^6-(1-iminoethyl)-lysine dihydrochloride (L-NIL) can attenuate circulatory failure and multiple organ injury in a rodent model of septic shock.

Male Wistar rats were anaesthetized with thiopental 120 mg kg^{-1} i.p. The trachea, carotid artery, femoral and jugular veins, and bladder were cannulated. At 15 min after surgery, animals received *E. coli* lipopolysaccharide (LPS) 6 mg kg^{-1} i.v. followed by infusion of saline 6 ml kg^{-1} h^{-1}. At 2 h after LPS, the infusion was either maintained (control, n=10) or replaced by a bolus dose (3 mg kg^{-1}) and then infusion of L-NIL 3 mg kg^{-1} h^{-1} (n=8) in an equal volume of saline. Another two groups of rats not receiving LPS were given infusions of either vehicle (saline, n=10) or L-NIL (n=6). Animals were monitored for 6 h. Blood was obtained for measurement of indices of organ injury and total nitrite–nitrate concentrations.

Endotoxaemia for 6 h resulted in significant hypotension, tachycardia, renal, liver and pancreatic dysfunction–failure, and a marked increase in plasma total nitrite and nitrate concentrations. L-NIL significantly reduced total nitrite–nitrate concentrations and significantly attenuated delayed hypotension at 6 h after LPS The increases in serum concentrations of urea and creatinine (renal dysfunction), bilirubin, aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transferase (liver injury), and lipase (pancreatic injury) were not attenuated by L-NIL.

We conclude that selective inhibition of iNOS activity with L-NIL resulted in restoration of arterial pressure, significant inhibition of the increase in plasma nitrate–nitrite concentrations but did not prevent multiple organ dysfunction–injury caused by endotoxin in the rat.

Keywords· complications, septic shock, rat

Effect of inhaled nitric oxide therapy on inflammatory response within the lung in ALI

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The use of exogenous inhaled nitric oxide therapy has become widespread in acute lung injury (ALI) Inflammatory mediators in bronchoalveolar lavage (BAL) fluid are thought to be important markers of the inflammatory process in ALI but the effect of inhaled nitric oxide on these mediators in the lung is unknown Our aim was to study the effect of exogenous nitric oxide therapy on the inflammatory response in the lung in ALI.

After obtaining approval from the Ethics Committee, we studied 30 patients with ALI, allocated randomly to either conventional ventilator therapy (n=15) or conventional therapy and inhaled nitric oxide (n=15). BAL fluid was collected at time 0, 24 and 72 h. IL-8, elastase, myeloperoxidase (MPO) and leukotriene B$_4$ and CDE$_4$ in BAL fluid were measured by ELISA. Patients were followed for 30 days or until death.

Mortality rate was 47% in the control group and 53% in the treatment group (P=0.76) and mean length of ICU stay was the same in both groups (19.1 days). The number of patients with resolution of ALI was similar in both groups but mean length of time to resolution of ALI was 7.5 days in the inhaled nitric oxide group and 12.4 days in the control group (P=0 006). There was a mean 47% improvement in Pa_{O_2} on introduction of inhaled nitric oxide therapy. There was no difference between control and treatment groups for IL-8, elastase or MPO concentrations in BAL fluid over the 72-h study. Leukotriene B$_4$ and CDE$_4$ concentrations increased in the inhaled nitric oxide group at 72 h (P=0 03 and P=0 03) MPO concentrations at time 0 were higher in patients who died than in those who survived (P=0 04)

Inhaled NO also reduced time to resolution of ALI and thus ventilatory time was reduced. Despite increased leukotriene concentrations in BAL fluid, inhaled NO therapy did not seem to effect any other inflammatory markers in ALI MPO may be a marker of prognosis in ALI. This work provides evidence of the efficacy of inhaled nitric oxide therapy without marked adverse effects on inflammatory processes

Acknowledgement

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Keywords: pharmacology, nitric oxide; complications, acute lung injury

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Effect of inhaled nitric oxide therapy on oxidant stress during ALI

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The use of inhaled nitric oxide therapy has become widespread in acute lung injury (ALI) despite no evidence that it improves mortality. It is thought that the oxidant–antioxidant balance in ALI may be important and it has been shown that plasma lipid peroxides (LPO) are increased in ALI. It is also thought that feedback inhibition of nitric oxide synthase (NOS) activity during inhaled nitric oxide therapy may explain rebound phenomena on inhaled nitric oxide withdrawal, but this has still to be demonstrated Our aim was to study the effect of exogenous nitric oxide therapy on oxidant stress in ALI.

After obtaining approval from the Ethics Committee, we studied 30 patients with ALI, allocated randomly to either conventional ventilator therapy (n=15) or conventional therapy with inhaled nitric oxide (n=15). Serum and bronchoalveolar lavage (BAL) fluid were collected at time 0, 24 and 72 h. Patients were followed for 30 days or until death. Total serum nitrate and nitrite concentrations were measured using the Greiss reaction, LPO using a colorimetric assay and BAL leucocyte NOS activity using a spectrophotometric technique at 413 ηm.

Serum total nitrate and nitrite concentrations increased in the presence of inhaled nitric oxide therapy (P=0.02) but not in the control group (P=0.67). Serum LPO did not change in either group over the 72-h period (P≥0 3). NOS activity decreased in the inhaled nitric oxide group (P=0.01) but not in the control group (P=0 2)

The increase in serum total nitrate and nitrite concentrations demonstrates the importance of this metabolic pathway in the metabolism of nitric oxide. The lack of change in serum LPO suggests that there is no significant increase in total body oxidant stress during inhaled NO therapy. Down regulation of endogenous NOS activity could explain the rebound phenomena on withdrawal of inhaled nitric oxide.

Acknowledgement

BHC is supported by the Royal College and Association of Anaesthetists scholarship.

Keywords: pharmacology, nitric oxide; complications, acute lung injury

POSTER PRESENTATIONS

Serum albumin and colloid osmotic pressure in survivors and non-survivors of critical illness

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We have compared changes in albumin and colloid osmotic pressure (COP) over time between survivors and non-survivors who stayed in the ICU for at least 7 days.

Data were retrieved by retrospective analysis of ICU and biochemistry databases. All patients had daily measurements of albumin concentrations and twice weekly COP measurements throughout ICU admission. They received crystalloid and colloid infusion, and parenteral and enteral feeding. Infusion of albumin was not used except that coincidentally present in blood products used to correct haematological abnormalities.

We studied 145 patients (66 non-survivors, 79 survivors). Non-survivors were significantly older (mean age 58 yr) than survivors (49 yr). There was no significant difference in APACHE II (mean 18 for non-survivors; 22 for survivors), sex or length of stay (median 14 days for non-survivors; 15 days for survivors).

Regression analysis of mean COP and albumin revealed that albumin contributed 17% towards COP in these patients.

There was a similar decrease in albumin in non-survivors and survivors (table 4), which may reflect the inflammatory response or haemodilution, or both. However, survivors showed an ability to increase serum albumin concentrations possibly as a result of resumption of synthesis. COP varied little between or within groups, possibly because of the use of artificial colloids (predominantly Gelofusin). There was no relationship between death and COP.

Keywords: intensive care; protein, albumin; blood, colloid osmotic pressure

Changes in plasma antioxidant potential in aortic aneurysm surgery

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We have assessed changes in plasma antioxidant potential (PAP) after elective and emergency aortic aneurysm (AAA) surgery and investigated possible causes for these changes.

In patients undergoing AAA surgery, plasma was obtained before surgery, after operation following stabilization in the ICU, daily during ICU admission and 3 days after ICU discharge. Anaesthesia followed a standard protocol and use of propofol and mannitol was avoided. PAP, albumin, urate and bilirubin concentrations were measured in each sample. PAP was measured by assessing the ability of plasma to impede an oxidative process *in vitro*.

We studied 25 patients (elective: 15 survivors, two non-survivors; emergency: four survivors, four non-survivors). Mean age was 75 yr and mean APACHE II score 14 (SD 5.6). Mean preoperative PAP was 45.2 (SD 6.8) %, which is below the previously determined normal range (55–65%). The ratio of postoperative to preoperative values revealed a decrease in both PAP (0.78 (SD 0.12)) and albumin (0.68 (0.20)) relative to baseline (=1.00), unlike urate (0.97) and bilirubin (1.65). Regression analysis of the decrease in PAP showed no significant dependence on cross-clamp time, blood loss, transfusion volume or fluid replacement volume. However, 60% of the change in PAP was associated with change in albumin ($P<0.001$). PAP recovery was 0.90 of baseline (IQR 0.80–1.00) by 5 days after surgery. Further regression analysis of this recovery showed an association between the increase in PAP and albumin values (53%, $P<0.001$).

Plasma antioxidant potential appeared to be low before surgery, which is consistent with studies showing reduced antioxidants in vascular disease. During surgery there was a decrease in PAP that was strongly associated with a decrease in albumin. It was not related to any measure of dilution or length of ischaemic cross-clamping. PAP approached preoperative values by 5 days after surgery.

Keywords: surgery, vascular; blood, antioxidants

Rapidly progressive loss of muscle mass in the critically ill

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Muscle wasting is common in critically ill patients and may lead to severe weakness. This may cause prolonged ventilator dependence and delayed hospital discharge. We investigated prospectively the severity of muscle loss in patients expected to stay in the ICU for more than 2 weeks.

A muscle biopsy was obtained from the vastus lateralis under local anaesthesia within the first 48 h in the intensive care unit (ICU). The procedure was repeated at weekly intervals up to a maximum of three biopsies. Samples were subjected to morphometric analysis to obtain mean fibre diameter for type I and II muscle fibres.

Mean (SD) fibre diameters are shown in table 5. Median APACHE II score was 17 (range 8–36) and median organ failures were 3 (1–5).

Differences between the first and second and between the first and third biopsies were significant ($P<0.05$) for both fibre types (paired *t* test).

Table 5 Mean (SD) fibre diameters (μm)

	Type I	Type II
Patients with two biopsies (n=13)		
1st biopsy	55.5 (8.5)	49.5 (10.8)
2nd biopsy	46.5 (7.0)	42.0 (9.3)
Patients with three biopsies (n=5)		
1st biopsy	46.0 (11.1)	41.4 (14.9)
3rd biopsy	33.8 (4.1)	29.0 (8.9)

Table 4 Albumin concentrations and colloid osmotic pressure (COP) in survivors (S) and non-survivors (NS). Values are mean (SD) or median (IQR). *$P<0.05$, **$P<0.01$

Albumin (g litre^{-1})	Mean	Minimum	Time to minimum	Mean after minimum
NS	15.7 (5.1)*	10.3 (4.4)	5 (2–8)	18.6 (5.3)**
S	18.3 (4.6)	12.3 (4.4)	7 (3–14)	13.3 (5.1)
COP (mm Hg)	Mean	Minimum	Mean after minimum	
NS	19.1 (2.8)	16.3 (2.7)	18.1 (3.1)**	
S	18.7 (2.4)*	16.0 (2.3)	17.8 (2.6)	

In summary, there was rapid progressive loss of muscle mass in critically ill patients. Patients lost approximately 16% of muscle mass within the first week and 28% of muscle mass within the first 2 weeks. This approximates to 8.4 kg of muscle per fortnight.

Keywords: intensive care; muscle skeletal, loss

Muscle protein synthesis and glutamine concentrations after caecal ligation and puncture (CLP) in the rat

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Muscle glutamine depletion may depress protein synthesis. We measured changes in muscle protein synthesis and glutamine in a rodent model of sepsis.

Male Wistar rats were allocated randomly to groups of similar mean weight. Three groups underwent CLP and three laparotomy (LAP). Surviving animals were sacrificed at 24, 72 or 96 h. Rats were killed at the start of the experiment and at 96 h as controls. Rates of protein synthesis (Ks) were measured by the "flooding dose" technique. Muscle glutamine (gln) concentrations were measured by HPLC. Results are presented as mean (SEM). Statistical analysis was by analysis of variance.

Changes in gln and Ks for each group are shown in table 6. Muscle gln was 5.85 (0.2) μmol g^{-1} at the start of the study and 4.75 (0.28) μmol g^{-1} at the end ($P<0.05$); Ks was 7.48 (0.25) at the start and 6.45 (0.33) at the end in the control rats ($P<0.05$).

Table 6 Changes in protein synthesis (Ks) and glutamine (gln) concentrations (μmol g^{-1}) after caecal ligation and puncture (CLP) or laparotomy (LAP) (mean (SEM)). *$P<0.0001$ compared with t0; †$P<0.01$ compared with LAP

	24 h	72 h	96 h
CLP gln	3.31 (0.12)*†	2.15 (0.14)*†	2.07 (0.26)*†
LAP gln	4 04 (0.30)*	3.33 (0.20)*	3.42 (0.25)*
CLP Ks	3.28 (0.2)*†	2.87 (0.24)*	3.33 (0.21)*
LAP Ks	5.03 (0.39)*	3.25 (0.31)*	2.66 (0.16)*

Although both gln and Ks were reduced after CLP and LAP, the relationship between them was inconsistent in this model.

Keywords: protein, synthesis; protein, amino acids; surgery, laparotomy; rat

Quality of albumin from sepsis patients

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Septic shock is frequently accompanied by a decrease in the antioxidant activity of plasma. Albumin constitutes a substantial part of the normal antioxidant activity of plasma, and so part of the decrease in antioxidant activity in septic shock may be caused by concomitant loss of albumin. We have examined the antioxidant quality of serum albumin from a septic patient in comparison with albumin from a normal subject.

Albumin was purified from plasma using Heparin-Sepharose, Cibacron Blue and hydroxyalkoxypropyl dextran. The redox active sulphydryl group activity was measured by titration with 5,5'-dithiobis(2-nitrobenzoic acid). The ability of each albumin sample to reduce phospholipid hydroperoxides was assessed by high pressure liquid chromatography.

The redox active cysteine 34 in human serum albumin was partly oxidized. The amount of reduced sulphydryl group was 0.40 and 0.33 mol/mol in normal and septic subjects, respectively, whereas the reduction in phospholipid hydroperoxides was 0.07 nmol min^{-1} mg^{-1} in both groups. The reduction in phospholipid hydroperoxides is a protective mechanism against lipid peroxidation. The value for albumin reduction of phospholipid hydroperoxides is novel and has not been reported previously.

These preliminary results suggest that although albumin may be lost from the circulation, the quality of the remaining albumin is not compromised in septic patients. The clinical value of maintaining plasma antioxidant potential in the face of a septic insult has yet to be established.

Keywords: protein, albumin; complications, sepsis

Urine and plasma cytokine concentrations in the critically ill

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We have investigated urine and plasma cytokine concentrations in critically ill adults to establish which, if any, are excreted by the kidney.

We studied 14 patients (mean age 54 yr, median APACHE II 14.5). Eleven patients had severe sepsis and three had the systemic inflammatory response syndrome. Matched blood and urine samples totalling 27 sample pairs were obtained at weekly intervals. Blood was collected into lipopolysaccharide (LPS)-free tubes containing disodium ethylenediaminetetraacetic acid (EDTA). Urine was collected into sterile containers. After immediate centrifugation at 4°C at 4000 rpm, the supernatants were stored at –70°C.

Tumour necrosis factor alpha (TNF-α), soluble TNF receptors (sTNFR) I and II, interleukin-1β (IL-1β), IL-1 receptor antagonist (IL-1ra), and IL-4, IL-6, IL-8, IL-10 and IL-13 were assayed by specific enzyme-linked immunosorbent assays (ELISA) (R&D Systems, Abingdon, Oxon, UK).

Urine and plasma concentrations of IL-6, sTNFRI, sTNFRII, IL-1ra and plasma IL-10 were greater than the upper limit of the assays, and were 10, 500, 500, 1000 and 50 pg ml^{-1}, respectively Mean TNF-α concentrations were 6.5 (range 0.5–65.1) pg ml^{-1} in urine and 4.3 (0.4–18.5) pg ml^{-1} in plasma. Mean IL-13 concentrations were 85.0 (40.5–146.3) pg ml^{-1} in urine and 60.9 (20.6–173.7) pg ml^{-1} in plasma. IL-β, IL-4 and IL-8 were undetectable in urine and plasma.

Our findings suggest that in these patients with severe sepsis or SIRS, TNF-α, sTNFRI, sTNFRII, IL-1ra, IL-6, IL-10 and IL-13 were excreted in urine and confirm previous findings that these cytokines are increased in plasma.

Keywords: polypeptides, cytokines; complications, sepsis

Outcome of mechanical ventilation for exacerbations of chronic airflow limitation

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We have determined if the pessimism surrounding the intensive care of patients with chronic airflow limitation is justified by outcome

We conducted a retrospective audit from the North East Thames intensive care unit (ICU) audit database of patients with admission codes of COAD and asthma to compare with all patients in the database. Mean results are shown in table 7.

Table 7 Audit of database of patients with admission codes of chronic obstructive airways disease (COAD) or asthma compared with all patients in the database. Mean results are shown

	All patients	COAD	Asthma
n	20547	344	319
Age (yr)	57	67	39
ICU length of stay (days)	3.5	7.1	3.8
Hosp. length of stay (days)	19.1	21.2	14.5
ICU mortality (%)	18	21	6
Hosp mortality (%)	24	35	11
SMR	1.13	0.99	0.93

Two-thirds of asthmatic patients underwent ventilation for less than 48 h, whereas 50% of patients with chronic airflow limitation required more than 48 h support.

Patients with chronic airflow limitation were older than average ICU patients and spent twice as long in the ICU. Their ICU mortality was the same as other ICU patients but there was excess mortality on the ward. Undue pessimism about patients with chronic airflow limitation is difficult to justify.

Keywords: ventilation, mechanical; intensive care, audit; lung, chronic obstructive airways disease

Effect of lipoteichoic acid infusion on the pulmonary circulation in the anaesthetized pig

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There is recent evidence that lipoteichoic acid (LTA), a component of the gram-positive bacterial cell wall, is a mediator of sepsis.[1] Our objectives were to investigate the effect of LTA in pigs and to develop a large animal model of gram-positive sepsis.

Ten Landrace pigs, mean weight 22.3 (SD 2.1) kg, were anaesthetized. Ventilation was adjusted to maintain Pa_{CO_2} within physiological limits and to avoid hypoxia. The left common carotid artery and internal jugular vein were cannulated and a pulmonary artery catheter was positioned via the right external jugular vein. After removal of the anterior chest wall, the heart was suspended in a pericardial cradle. All animals received warm 0.9% saline solution to maintain pulmonary artery occlusion pressure at baseline. After stabilization five pigs received an infusion of LTA 250 µg kg^{-1} over 30 min and five pigs received an equal volume of 0.9% saline. The Mann–Whitney *U* test was used for statistical comparisons.

Mean pulmonary artery pressure (MPAP) at baseline was 22.4 (SD 3.4) mm Hg in the LTA group and 20.2 (2. 8) mm Hg in controls. After 30 min, MPAP had increased to 37.0 (4.5) mm Hg in the LTA group but was unchanged in controls (19.2 (1.3) mm Hg) ($P<0.01$ LTA *vs* controls at 30 min). In the LTA group, mean pulmonary vascular resistance index increased from 122.8 (58.5) mm Hg kg min litre^{-1} at baseline to 294.6 (109.6) mm Hg kg min litre^{-1} at 30 min; control values were 107.5 (37.9) and 88.36 (20.0) mm Hg kg min litre^{-1} ($P<0.01$, LTA *vs* controls at 30 min).

Our finding that LTA caused an increase in pulmonary vascular resistance and pulmonary artery pressure in pigs supports the existing evidence that LTA is a mediator of gram-positive sepsis.

Keywords: lung, blood flow; complications, sepsis; pig

References

1. De Kimpe SJ. *British Journal of Pharmacology* 1995; 114: 1317–1323.

Implications of methicillin-resistant *Staphylococcus aureus* in a general intensive care unit

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is an increasing problem in hospital practice, and in the ICU in particular. We have investigated the hypothesis that MRSA occurs in patients with a longer ICU stay and a higher mortality. We have also investigated the frequency of interventions in patients with MRSA compared with controls matched for APACHE II score and risk of death.

MRSA was cultured on admission or during ICU stay from 35 patients over a 2-yr period. They had 46 out of a total of 976 admissions. Each patient was matched for APACHE II score and risk of death with a MRSA-free control. There was no difference in ICU or hospital mortality (chi-square test) (table 8).

MRSA patients stayed in the ICU for longer than matched controls, and required interventions for longer (inotropes, PA catheters, antibiotics, TPN and enteral nutrition). This has significant financial implications. In contrast with other studies, we found no difference in either ICU or hospital mortality between MRSA patients and controls after admission risk adjustment.

Table 8 Patient and mortality data in the methicillin-resistant *Staphylococcus aureus* (MRSA) and control groups. *$P<0.05$, **$P<0.01$

Variable	MRSA group	Control group
n	35	35
Mean age (yr)	54.8	59.7
Median length of stay (days)	31**	5
Mean APACHE score	22.2	22.4
Mean risk of death (%)	40.5	42.1
Median daily TISS	26.4	26.7
Died in ICU (*n*)	7	7
Died on ward (*n*)	7	3
Discharged from hospital (*n*)	21	24
Interventions (total No. of days)		
Inotropes	217*	95
PA catheter	232*	119
Antibiotics	667**	299
TPN	500**	163
Enteral nutrition	409**	203

Keywords: intensive care, audit; intensive care, infection

Dosing regimens for nebulized gentamicin in intensive care

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We have assessed two nebulized gentamicin dosing regimens in terms of respiratory and cardiovascular variables, and plasma and sputum concentrations.

We studied 12 patients, without renal failure, requiring orotracheal mechanical ventilation for 3 or more days, allocated randomly to receive gentamicin 2 mg kg^{-1} 12-hourly (group A) or 1 mg kg^{-1} 8-hourly (group B) via a standard nebulizer from a 7200a Puritan Bennett ventilator over 30 min. On days 1 and 3, respiratory and cardiovascular variables were recorded before and 30 min after one administration, while corresponding sputum samples were obtained at 1, 2, 4, 6 and 12 h (group A) and 1, 2, 4, 6 and 8 h (group B). Plasma samples were obtained daily at 240 min after dosing. Frequency data were compared using Fisher's exact test. Trough sputum concentrations were compared between groups using the Mann–Whitney Wilcoxon test, as were respiratory and cardiovascular variables before and after administration. Significance was taken at $P=0.05$.

The groups were similar in patient characteristics. Nebulization did not result in significant changes in physiological measurements. Both groups had similar plasma concentrations with none greater than 1 mg litre^{-1}, but group B was significantly more likely to have undetectable plasma concentrations than group A (six of 18 and one of 17, respectively). Both groups had a similar incidence of peak sputum concentrations outside the range of the assay (1250 mg litre^{-1}). Trough concentrations were highly variable and not significantly different from day 1 to day 3 within or between groups (table 9).

Table 9 Median (range) trough sputum concentrations (mg litre^{-1}) in each group

	Day 1	Day 3
Group A	61 (16–158)	108 (75–741)
Group B	19 (13–395)	52 (10–279)

Using a minimum inhibitory concentration for *Pseudomonas aeruginosa* of 4 mg litre^{-1} as the target, administration of gentamicin 1 mg kg^{-1} 8-hourly produced high sputum concentrations with minimum plasma concentrations.

Keywords: Intensive care; intensive care, infection; antibiotics, gentamicin

Table 10 Pharmacokinetics of ceftazidime in patients and healthy volunteer (mean (SD)). AUC=Area under the curve; *Cl*=clearance. [a]AUCss, [b]AUC∞ and using 1g dose. *$P<0.05$ compared with healthy volunteers (unpaired Student's *t* test)

	AUC (mg h litre^{-1})	*Cl* (litre h^{-1})	Volume of distribution (litre)	Half-life (β) (h)
Patients	274.4 (141.5)[a]	9.3 (5.0)	58.3 (27.0)*	4.8 (1.9)*
Healthy volunteers	153.5 (23.1)[b]	6.6 (1.0)	13.6 (1.9)	1.8 (0.1)

Altered ceftazidime pharmacokinetics in critically ill patients

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The pharmacokinetics of ceftazidime in critically ill patients are likely to be different from those in healthy volunteers because of possible changes in volume of distribution and clearance. Our objective was to evaluate these potentially altered pharmacokinetics.

We studied 15 adults, median APACHE II score 13 (interquartile range 4), with normal serum creatinine concentrations (mean 78 (SD 21) μmol litre^{-1}) receiving ceftazidime 2 g i.v. 8-hourly. Blood samples were obtained at time points during one dose interval (8 h), centrifuged, separated and frozen. Serum ceftazidime concentrations were assayed by high pressure liquid chromatography.

Pharmacokinetic analysis was performed by computer (WinNONLIN software) using a non-compartmental method and compared with values obtained from healthy volunteers (table 10).[1]

In this group of critically ill patients, the elimination half-life of ceftazidime was prolonged significantly because of a large increase in volume of distribution.

Keywords: intensive care; antibiotics, ceftazidime

Reference

1. Wise R. *Journal of Antimicrobial Chemotherapy* 1981; 8: 277–282.

Effect of inter-hospital transfer on the general intensive care patient

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The absence of a vacant intensive care bed in the local hospital should not adversely affect critically ill patients. We have investigated how this ideal was almost achieved between 1993 and 1996.

The South Thames (West) intensive care database collects data from 15 general intensive care units in the former South West Thames Region using a common computer program and independent validation for accuracy of recorded data; 6332 non-surgical general intensive care patients were analysed retrospectively for severity of illness using APACHE III score. The APACHE III primary system failure definitions were used. Survival to leave the reporting hospital was the outcome measure. Scores were compared by *t* test and outcomes by chi-square.

The largest four groups only are shown for clarity (table 11).

Table 11 APACHE III score and mortality of transferred (Tr) and non-transferred (NT) non-surgical general intensive care patients in the four largest groups (cardiac, respiratory, GI and neurological). *$P<0.05$

	Total		Cardiac		Respiratory		GI		Neurological	
	Tr	NT	Tr	NT	Tr	NT	Tr	NT	Tr	NT
n	585	5747	124	2634	206	1213	118	764	50	457
Score	62.7	61.5	72.1*	61.3	60.7	63.1	59.1	55.8	69.5	68.3
Mortality (%)	32.6	32.5	46.8*	34.0	28.2	34.6	22.9	18.7	38.0	43.1

The data showed that patients with primarily cardiovascular diagnoses were sicker and had a higher mortality than those in other groups. This implies that either a higher threshold for ICU admission is being used if transfer is necessary or patients in this group deteriorated during transfer.

Keywords: Intensive care, audit; intensive care, transfer

Impact of a high dependency unit on the workload of an intensive care unit

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We have assessed the impact of opening a high dependency unit (HDU) on the workload of an adult general intensive care unit (ICU).

Patients were enrolled during the 6 months before and 6 months after opening the HDU. Patient details, severity of illness (APACHE II), diagnosis and outcome were recorded prospectively. Bed occupancy was determined on a daily basis; 430 patients were admitted to the ICU and 641 to the new ICU–HDU complex (49% increase). Patients nursed in the new HDU were older than HDU patients nursed in the ICU (mean 61 *vs* 53 yr) and stayed longer (median 0.92 *vs* 0.85 days). For critically ill patients managed in the ICU, illness severity decreased after the HDU opened (median APACHE 13 *vs* 15). Duration of stay was shorter (median 1.44 days compared with 1.54 days before opening the HDU). More HDU patients were admitted electively after the HDU opened (55% *vs* 43%) with no change in admission source for HDU patients. Only 14% of HDU admissions were transfers from ICU. Weekly occupancy of the ICU and HDU were variable. There were matching peaks and troughs on HDU and ICU occupancy over some months as HDU facilities were reduced as demand for ICU beds increased. ICU occupancy decreased after the HDU opened (77–71%). Occupancy of HDU beds increased by 35–61% and was lower at the weekend. The cancellation rate for major operations decreased from 28 in the 6 months before opening the HDU to 18 in the 6 months after.

Expanding critical care services resulted in increased demand, mainly for HDU care after elective surgery. These results suggest that the overall severity of illness of patients in hospital may have decreased, as judged by decreasing severity in ICU. Overall expenditure on these services is unlikely to fall.

Keywords: Intensive care; intensive care, audit

Impact of consultant surgeon appointments on intensive care workload

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Between 1993 and 1996, there were six new consultant surgeon appointments (four additional and two replacement posts) at Leicester General Hospital (LGH) NHS Trust, a teaching hospital where the surgeons are organized into two teams. To coincide with these surgical appointments there were no targeted increases in funded beds in the intensive care unit (ICU). It was thought that after each new appointment there would be a redistribution of work within each team of surgeons. We assessed the impact of these changes on ICU workload.

We reviewed the number of ICU admissions and ICU bed days for each team in the 6-month period before and after the arrival of the first patient of each new consultant surgeon.

After the appointment of the additional surgeons, there were significant increases in the number of ICU admissions (7.3–9.9/month) and ICU bed days (36–53.7/month) for the new surgeon's team ($P<0.01$, Mann–Whitney). However, after the appointment of the replacement surgeons, there were no significant changes in the number of ICU admissions (8.1–7.6/month) or ICU bed days (40.8–36) for the replacement surgeon's team.

The appointment of additional consultant surgeons resulted in an increase in demand for ICU resources. There were no resource implications after the appointment of the replacement surgeons. As there were no targeted increases in ICU resources over the same period of time, this resulted in an increase in the number of refused admissions, inter-unit transfers and an increase in the competition for beds for major elective surgery. In response to this there has as been an expansion in ICU resources.

Keywords: intensive care, audit; intensive care, workload

A critical care liaison service

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Faced with an increasing demand to admit patients to a limited number of intensive care beds, a critical care liaison service aimed at bringing specialist skills to critically ill patients on general wards was set up at our hospital. Our results are reported.

Indices based on simple clinical measurements and considered indicative of serious physiological disturbance were identified: heart rate <45 or >125 beat min^{-1}, systolic arterial pressure <90 mm Hg, ventilatory frequency <8 or >30 bpm, Sp_{O_2} <90% on 24% oxygen, Pa_{O_2} <9.0 kPa, Pa_{CO_2} >6.5 kPa on 24% oxygen, pH <7.25 and Glascow coma scale <8 or a decrease >2 points.

Patients meeting any one of these criteria were notified to the intensive care unit (ICU) and subsequently assessed by a senior intensive care physician.

We studied 18 patients over a 4-month period; five patients (27%) were treated successfully on the ward. Admission to the ICU was considered inappropriate in another five patients. Eight patients were admitted to the ICU (six were discharged back to the ward after successful treatment). The majority of calls (72%) followed deterioration in respiratory status. All calls apart from one were received before midnight.

The establishment of a critical care liaison service promoting early recognition and treatment of seriously ill patients on the ward has resulted in a reduction in the number of non-essential ICU admissions by optimizing the quality of patient care outside the ICU.

Keywords: Intensive care, audit

As seen on TV: cardiopulmonary resuscitation and television dramas

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The advent of prompt resuscitation and ready availability of intensive care have produced moral dilemmas concerning the appropriateness of cardiopulmonary resuscitation (CPR). If patients and relatives are to become more involved in decision making, they require accurate and clear information. The background CPR knowledge of the public has been shown to be derived from television. The portrayal of successful CPR on television may influence the demand for resuscitation. Patient desire for resuscitation and intensive care is influenced by expected outcome. To explore television as a source of knowledge, we analysed resuscitation attempts portrayed in four popular television medical dramas with frequent emergencies. The UK viewing figures were 8–14 million.

We viewed a total of 73 episodes of "Cardiac Arrest" (World Productions), "Medics" (Granada), and "999" and "Casualty" (BBC). For each occurrence of cardiac arrest, the following were analysed: whether CPR was undertaken, initial outcome, estimated age group of the patient, sex, presumed diagnosis, CPR sequence and on-screen death (table 12).

Table 12 Occurrence of cardiac arrest in 73 episodes of four TV medical dramas ("Cardiac Arrest", "Medics", "999" and "Casualty")

TV programme	Episodes	Arrests	Resuscitations	Success
999	9	6	6	6
Casualty	26	18	11	1
Cardiac Arrest	27	29	16	4
Medics	11	5	5	2
Total	73	58	38 (65%)	13 (34%)

The British programmes gave immediate success rates comparable with the UK BRESUS study of 3765 arrests. Despite this, the public remains overoptimistic about the likely outcome. This may be because of a natural reluctance to believe that not all medical interventions are successful. Alternatively, these programmes form only a small part of the total exposure of the public to dramas featuring critical illness.

Keywords: heart, resuscitation

Employment of a resuscitation training officer improves delivery of cardiopulmonary resuscitation in a district general hospital

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We have assessed the effect of the arrival of a resuscitation training officer (RTO) on the delivery of cardiopulmonary resuscitation (CPR) in a district general hospital (DGH).

We performed a two-stage audit of all arrest calls over two 3-month periods before and 9 months after employment of the RTO. The duty intensive care anaesthetists completed an audit form for all hospital cardiac arrests attended.

The first stage audit covered 92 arrests, the second 67. The number of inappropriate calls decreased from 20% to 2%. However, 18% of appropriate calls in the second audit did not warrant treatment. Effective initial airway management, as assessed on arrival of the anaesthetist, improved from 41% to 81% (P=0.000001). Advanced life support (ALS) guidelines were present at all arrests in the second audit compared with 32% previously. Although ALS guidelines were followed in 85% of arrests in the second audit (an increase from 79%), this was not statistically significant. However, nursing staff applied BLS guidelines appropriately in 91% of cases in the second audit. Equipment faults were the same (15% *vs* 16%); 50% of these faults were beyond the control of the RTO.

After a period of only 9 months in post, an RTO can achieve significant improvements in the delivery of CPR. These were found to be greater in areas subject to nursing jurisdiction (e.g. BLS) and less in those of predominately medical staff jurisdiction (e.g. "do not resuscitate" orders and ALS). This may reflect the concentration on nurse education in the initial phase of the post.

Keywords: intensive care, audit; heart, resuscitation

Long-term outcome of patients treated in a district general hospital intensive care unit after severe sepsis or SIRS

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Once a patient has improved adequately to be discharged from the ICU, there is, at present, only sporadic documentation of outcome. There is only anecdotal evidence of problems long after a patient has left the ICU. Over the past 4 yr, we have set up a follow-up programme in Reading to determine the long-term problems after critical illness in our ICU patients.

Data were collected on patients admitted to the ICU with a diagnosis of multiple organ failure (MOF) secondary to sepsis or systemic inflammatory response syndrome (SIRS) in a 12-month period from 1995 to 1996. Mortality data were recovered from the ICU, within the hospital after discharge from the ICU and within 1 yr. All surviving patients with a length of stay greater than 4 days were invited to attend a follow-up clinic at 2, 6 and 12 months after discharge. In the clinic, indices of physical and psychological recovery were monitored and, where appropriate, referrals arranged.

The results were as follows: (1) mortality: 46% of patients died in the ICU, 7% died in hospital after discharge from the ICU and 4% died within 1 year of discharge from the ICU; (2) morbidity: problems associated with tracheostomy (30%), abnormal lung function at 1 yr (45%), impaired creatinine clearance at 1 yr (33%) and post-traumatic stress disorder (PTSD) (55%); (3) referrals: 26 referrals were made for 11 patients, including to ENT surgeons, PTSD counsellors and chronic pain specialists.

Both mortality and morbidity were high in this group of ICU patients and many of the survivors needed further specialist referral. Therefore, we feel an "intensive after-care" approach after "intensive care" is an important area for future development by ICU staff.

Keywords: intensive care, audit; complications, sepsis

Audit of pulmonary artery catheter insertion and use in the first 24 h

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We have determined which grade of medical staff initiates insertion of a pulmonary artery catheter and how often the catheter is used within the first 24 h. This follows the recent controversy on the use and misuse of pulmonary artery catheters and anecdotal evidence that once inserted they are not used.

For 50 consecutive pulmonary artery catheters, we determined who requested insertion of the catheter, who inserted the catheter and how often it was used in the first 24 h after insertion. This was done without informing other members of staff on the unit to prevent any change in normal practice.

A total of 49 forms were completed, of which four were incomplete, leaving 45 available for analysis (table 13).

Table 13 Catheter use according to grade of medical staff

Grade of medical staff	Requesting catheter	Inserting catheter
Consultant	29 (64.4%)	2 (4.4%)
Senior registrar	7 (15.6%)	6 (13.3%)
Registrar	6 (13.3%)	20 (44.4%)
SHO	3 (6.7%)	17 (36.8%)

The catheter was used on average 3.8 times in the first 24-h period (range 1–10). The results of use showed that if the registrar placed the catheter of his own volition, it was used least often, while if the SR placed it, it was used most often. Five catheters were used only once in the first 24 h (four of these patients had liver failure and one cardiogenic shock).

The majority of pulmonary artery catheters were placed at the request of a senior member of staff, they were sited by more junior medical staff and they were used more often than anecdotal evidence would suggest.

Keywords: intensive care, audit; equipment, catheters

Use of remifentanil in the transfer of the critically ill

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We have evaluated the efficacy and safety of remifentanil during transfer of the critically ill.

We studied 10 ventilator-dependant patients requiring transfer. Normal transport practices and monitoring were adhered to but remifentanil was the sole sedative analgesic drug. A bolus of 1 $\mu g\ kg^{-1}$ followed by infusion of 0.5 $\mu g\ kg^{-1}\ min^{-1}$ was given. Measurements of heart rate, mean arterial pressure (MAP), arterial blood-gas tensions, ventilator settings, airway pressure and sedation score were obtained before, during and 10 min after cessation of infusion. Patients were excluded if they had uncontrolled arrhythmia, hypertension or hypotension, acute head injury, opioid hypersensitivity or were receiving long-term treatment with sedatives or opioids resulting in low sedation scores.

Sedation scores were reliably reduced during transfer and reverted to pre-transfer levels within 10 min of stopping remifentanil. MAP decreased initially after the bolus dose but responded rapidly to reductions in infusion rate and/or i.v. fluids. All MAP values returned to within 20% of pre-transfer values 10 min after transfer. Remifentanil alone allowed mechanical ventilation in all but one patient. Oxygenation did not deteriorate significantly and pre-transfer levels of ventilator dependence were attained 10 min after stopping the infusion.

Remifentanil provided reliable, rapidly reversible respiratory depression allowing mechanical ventilation without the use of neuromuscular blocking agents. Although MAP decreased after administration of the bolus dose, this effect was predictable and easily reversed. Sedation level increased or decreased rapidly, enabling accurate neurological assessment much earlier than previously possible.

Keywords: analgesics opioid, remifentanil; intensive care

Relationship between mixed venous oxygen tension, oxyhaemoglobin saturation and arterial oxygen tension in acute respiratory distress syndrome (ARDS)

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Mixed venous oxygen tension $P\bar{v}_{O_2}$ and mixed venous haemoglobin saturation ($S\bar{v}_{O_2}$) may influence arterial oxygen tension (Pa_{O_2}) by complex mechanisms. It has been stated that increases in cardiac output (CO) increase the degree of pulmonary venous admixture (*Qs*/*Qt*) and reduce Pa_{O_2}. I hypothesized that this might not be the case in ARDS where $S\bar{v}_{O_2}$ was less than 75%, whatever the level of CO

Table 14 Haemodynamic variables recorded before (T_1) and after (T_2) a therapeutic increase in oxygen delivery (mean (SD)). *$P<0.05$; **$P<0.01$ (T_1 compared with T_2)

CI (litre $min^{-1}\ m^{-2}$)	Pa_{O_2} (kPa)	$P\bar{v}_{O_2}$ (kPa)	$S\bar{v}_{O_2}$ (%)	Do_2 (litre $min^{-1}\ m^{-2}$)	OER (%)	*Qs*/*Qt* (%)	Pa_{O_2}/FI_{O_2} (kPa)
4.1	12.4	4.6	65.2	655	24.9	38.8	14.0
(0.8)*	(2.5)*	(0.5)*	(6.0)**	(135)**	(3.6)**	(3.7)	(4.5)**
5.1	15.7	5.6	74.4	817	18.5	38.4	21.6
(0.8)	(2.4)	(0.4)	(3.4)	(129)	(2.7)	(4.2)	(5.8)

Table 15 Clearance and urinary excretion of tumour necrosis factor alpha (TNF-a) and interleukin-13 (IL-13) in critically ill adults. Cl_c=Cytokine clearance, E_c=cytokine excretion (=urine flow × urinary cytokine concentration) and fractional excretion of cytokine ($F\text{EX}_c$) $=Cl_c/Cl_{Cr}$ (mean (range))

	Urinary concn (pg ml^{-1})	Clearance (Cl_c) (ml min^{-1})	Excretion (E_c) (pg min^{-1})	Fractional excretion ($F\text{E}_{Xc}$)
TNF-a	6.5 (0.5–65.1)	4.5 (0.1–29.6)	14.81 (0.7–225.8)	0.09 (0.0–0.5)
IL-13	85.0 (40.5–146.3)	4.1 (0.8–14.4)	193 (50.1–544.6)	0.1 (0.0–0.8)

because of the shape of the haemoglobin dissociation curve and the known ventilation to perfusion ratio ($\dot{V}/\dot{Q}$) abnormalities in ARDS.

We studied prospectively 10 patients with ARDS. All required a minimum $F\text{I}_{O_2}$ of 0.6 (mean 0.85) which was reduced by at least 0.1 during the study. Before (T_1) and after (T_2) a therapeutic increase in oxygen delivery ($D\text{O}_2$) the following variables were recorded: cardiac index (CI), Pa_{O_2}, $P\bar{v}_{O_2}$, $S\bar{v}_{O_2}$, $D\text{O}_2$, oxygen extraction ratio (OER), $Pa_{O_2}/F\text{I}_{O_2}$ ratio and $\dot{Q}s/\dot{Q}t$ (table 14).

In ARDS, where $S\bar{v}_{O_2}$ is less than 75% and if oxygen consumption remains constant, an increase in $P\bar{v}_{O_2}$ caused by an increase in $D\text{O}_2$ significantly increases Pa_{O_2}. The only other therapeutic option under these circumstances would be to alter ventilator settings to produce a very high $\dot{V}/\dot{Q}$ which is neither practicable nor safe. Difficulty in maintaining adequate Pa_{O_2} in ARDS is an indication for $P\bar{v}_{O_2}$ and $S\bar{v}_{O_2}$ measurement and manipulation.

Keywords: oxygen, tension; oxygen, saturation; lung, acute respiratory distress syndrome

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Renal clearance of TNF-a and IL-13 in critically ill patients

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In order to study the role of the functioning kidney in the elimination of inflammatory mediators, we have investigated clearance and urinary excretion of tumour necrosis factor alpha (TNF-a) and interleukin-13 (IL-13) in critically ill adults.

We studied 14 patients (mean age 54 yr, median APACHE II score 14.5). Eleven patients had severe sepsis and three had the systemic inflammatory response syndrome. Matched blood and urine samples totalling 27 sample pairs were obtained at weekly intervals. Blood was collected into lipopolysaccharide (LPS)-free tubes containing disodium ethylenediaminetetraacetic acid (EDTA). Urine was collected into sterile containers. Both were centrifuged immediately at 4°C at 4000 rpm and the supernatants stored at –70°C. TNF-a and IL-13 concentrations were assayed from plasma and urine by specific enzyme-linked immunosorbent assays (ELISA) (R&D Systems, Abingdon, Oxon, UK). Creatinine clearance (Cl_{Cr}), cytokine clearance (Cl_c), cytokine excretion (E_c=urine flow × urinary cytokine concentration) and fractional excretion of cytokine ($F\text{EX}_c=Cl_c/Cl_{Cr}$) were calculated using standard formulae (table 15).

Mean creatinine clearance was 66 (SD 38) ml min^{-1}.

TNF-a and IL-13, usually undetectable in the urine of normal subjects, appear to undergo renal elimination in patients with severe sepsis or SIRS.

Keywords: polypeptides, cytokines; intensive care

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CORRESPONDENCE

Propofol and postoperative nausea and vomiting

Editor,—I read with interest the article by Bree and colleagues[1] on combining propofol with morphine patient-controlled analgesia to prevent postoperative nausea and vomiting (PONV). They showed that addition of propofol did not decrease the incidence of PONV. I would like to suggest some explanations for their results.

The authors correctly pointed out that the plasma concentration of propofol for 50% reduction in nausea scores in a group of postoperative patients was 343 ng ml^{-1}.[2] This concentration may be achieved with a bolus dose of propofol 10 mg followed by continuous infusion of 1 mg kg^{-1} h^{-1}. Therefore, a 70-kg patient would receive 70 mg h^{-1}. In Bree and colleagues' study, the propofol treated group used a mean dose of propofol 9.8 (95% CI 7.5–12.1) mg h^{-1} for the first 24 h and 2.6 (95% CI 0.9–4.2) mg h^{-1} for the next 24 h. Indeed, the maximum dose of propofol used (in one patient) was 180 mg in a 4-h period (45 mg h^{-1}). Hence, it is likely that their patients received sub-therapeutic doses of propofol for antiemetic effects.

We have recently reported the use of patient-administered propofol for the treatment of PONV.[3] In a randomized, double-blind design, patients self administered propofol 20 mg or Intralipid (placebo) with a 5-min lockout interval, where no propofol could be administered. The propofol group had significant reductions in the degree of nausea (25% less nausea *vs* placebo), incidence of vomiting (12% *vs* 56%) and need for rescue antiemetic (17% *vs* 70%) compared with placebo. Placebo patients had a nine-fold increase in the risk of subsequent vomiting and a 10-fold increase in the likelihood of using rescue antiemetics. The propofol group received a mean dose of propofol 100±60 mg during the study (2 h). This was not associated with an increase in sedation compared with placebo. Propofol treated patients were also more satisfied with their control of PONV.

When propofol is used for its antiemetic effects in comparative studies, it is important that therapeutic dose ranges are administered.

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1. Bree SE, West MJ, Taylor PA, Kestin IG. Combining propofol with morphine in patient-controlled analgesia to prevent postoperative nausea and vomiting. *British Journal of Anaesthesia* 1998; 80: 152–154.
2. Gan TJ, Glass PSA, Howell ST, Canada AT, Grant AP, Ginsberg B. Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. *Anesthesiology* 1997; 87: 779–784.
3. Gan TJ, Glass PSA, Ginsberg B, Coleman R, Ray J. Propofol patient-controlled antiemesis is a safe and effective method for treatment of postoperative nausea and vomiting. *Anesthesiology* 1997; 87: A49.

Editor,—In our article we discussed the dose of propofol when combined with morphine for patient-controlled analgesia, and explained why it is unlikely that the dose of propofol given in this way would ever be sufficient to treat postoperative nausea and vomiting. The abstract published by Gan and colleagues[1] reported day surgery patients self administering either propofol 20 mg or 40 mg from a patient-controlled syringe driver. Patients were studied for 2 h and presumably would not have had major surgery and would not have been receiving regular opioid analgesics in addition to propofol. This treatment is unlikely to be of much practical use for the majority of patients and most anaesthetists would believe the technique unsafe for a general ward as it requires high dependency care.

I would hope that any peer-reviewed article from Gan and colleagues would temper the enthusiasm of the title of their abstract with some statistical caution. Forty-three patients received propofol in their study and there were no complications; this is compatible with a true incidence of serious complications of 6.9%,[2] which would be clinically unacceptable. The initial interest in using propofol to treat postoperative nausea and vomiting was because early reports suggested very low doses might be effective, and therefore simple techniques were safe for general use. I believe all the recent evidence suggests that this is not the case.

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1. Gan TJ, Glass PSA, Ginsberg B, Coleman R, Ray J. Propofol patient controlled anti-emesis is a safe and effective method for treatment of post-operative nausea and vomiting *Anesthesiology* 1998; 87: A49.
2. Hanley JA, Lippman-Hand A. If nothing goes wrong is everything all right? *Journal of the American Medical Association* 1983; 249: 1743–1745.

Anaesthesia in third world countries

Editor,—When asked to join a group of surgeons on a trip to rural Guinea, West Africa, we were faced with the challenge of providing safe general anaesthesia in a setting with certain limitations to anaesthetic practice. First, an unreliable electricity supply ruled out the use of any drug needing storage in controlled temperatures (e.g. propofol) and mains-operated equipment. Second, the lack of any gas-scavenging system made inhalation agents an inappropriate choice. Third, because of the shortage of trained staff, we had to ensure an awake patient at the end of each operation. Unfortunately, during their training, both authors had only gathered theoretical knowledge of the EMO inhaler, which is thought by many to be the ideal method of anaesthesia in third world countries.

Remifentanil, with its unique pharmacological profile, is used in different combinations to provide safe and easily titratable anaesthesia in many settings.[1–3] Methohexital is used frequently in our institution for awake sedation[4] and as propofol or inhalation agents were not thought to be an option for the reasons stated above, we decided to use the combination of remifentanil and methohexital as a simple i.v. anaesthetic regimen. The following technique was used successfully for general anaesthesia in 39 patients without any major complications.

After i.v. atropine 0.5 mg to block ketamine-induced secretions and to prevent bradycardia caused by remifentanil, patients received i.v. sedation with low-dose midazolam 0.05 mg kg^{-1} and ketamine 0.5 mg kg^{-1}. Anaesthesia was induced with a bolus dose of methohexital 1 mg kg^{-1} and an i.v. infusion was started containing methohexital 1 mg ml^{-1} and remifentanil 0.03 mg ml^{-1}, the initial rate being 1 ml kg^{-1} h^{-1} After mask ventilation was achieved, patients were given vecuronium 0.05–0.08 mg kg^{-1} and the trachea was intubated after 3–5 min. Patients underwent manual ventilation with 40% oxygen in air and the methohexital–remifentanil infusion was titrated to required effect during operation. Mean rate of infusion was 1.38 (range 0.7–1.95) ml kg^{-1} h^{-1}. The drip was turned off approximately 5 min before the end of operation and the majority of patients were awake and cooperative within 5 min of the end of the procedure. Postoperative analgesia was provided with an NSAID, alone or in combination with i.v. tramadol.

Details of the surgical procedures are given in table 1. Table 2 lists the choice of anaesthetic, its duration, time to extubation and complications encountered.

Table 1 Surgical procedures performed under general anaesthesia

Diagnosis	No. of anaesthetics
Hernia (inguinal, scrotal)	13
Goitre	9
Gun shot	5
Vesiculo-vaginal fistula	4
Utero-vaginal prolapse	4
Tubal abscess	2
Fixed tongue band	1
Appendicitis	1
Fractured elbow	1
Gluteal abscess	1
Lipoma	1
Perforated colon	1
Recto-vaginal fistula	1
Revision of vesicovaginal fistula	1

Table 2 Duration of anaesthesia, time to extubation and complications encountered

	No. of patients
General anaesthesia	
I.v. ketamine+spontaneous respiration	6
Remifentanil–methohexital + artificial ventilation	39
Duration of anaesthesia (min)	
Less than 30	4
30–60	15
60–90	14
90–120	4
120–180	6
Longer than 180	2
Time to extubation after stopping remifentanil–methohexital infusion (min)	
Less than 5	25
5–10	7
Longer than 10	5
Missing data	2
Complications	
Residual neuromuscular block	6
Nausea/vomiting	2
Respiratory arrest with i.v. sedation	1

There were no major problems with this technique. One critical anaesthetic incident occurred in a young woman who had received ketamine–midazolam sedation for revision of her gunshot wound, and experienced respiratory arrest when given another 20 mg of methohexital. The trachea was intubated and the patient recovered uneventfully, proving that a battery-powered pulse oximeter is a mandatory piece of equipment even in the most basic settings.

The cost of the general anaesthetic using remifentanil–methohexital is approximately £15 ($22) per hour of anaesthesia for a patient of 70 kg body weight. This relatively high cost is counterbalanced by the fact that the capital cost of an anaesthetic machine is not incurred.

We conclude that infusion of a fixed combination of remifentanil and methohexital provided safe and simple general anaesthesia. While not the method of choice in third world countries in standard hospital settings, we found it cost-effective and safe in an environment where anaesthesia needs to be provided with little equipment.

The mission to Guinea was organized by MANGO (Medical Actions in Guinea), a charity based in Frankfurt, Germany. All drugs were donated by the respective manufacturers.

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1. Burkle H, Dunbar S, van Aken H. Remifentanil: a novel, short-acting, μ-opioid. *Anesthesia and Analgesia* 1996; 83: 646–651.
2. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. *Anesthesiology* 1997; 86: 10–23.
3. Evans NT, Gunning KE, Park GR. Remifentanil for major abdominal surgery. *Anaesthesia* 1997; 52: 606.
4. Pottkämper C, Zickmann B, Wyderka T, Wulf K, Stertmann WA, Hempelmann G. Kurzzeitsedierung mit Propofol versus Brevimytal: Elektroenzephalometrische Quanti-fizierung von Wirkung und Wirkdauer. *Der Anaesthesist* 1996; 45 (Suppl. 2): A138.

Current practice of local anaesthesia for ocular surgery

Editor,—As anaesthetists at the King Khaled Eye Specialist Hospital (KKESH), we read with particular interest the survey "Current practice of local anaesthesia for routine ocular surgery," by Mawer and Coombes.[1] KKESH has completed 55 000 procedures under local anaesthesia and another 45 000 under general anaesthesia since its opening in 1984. We wish to endorse the recommendations of the Joint Working Party on Anaesthesia in Ophthalmic Surgery[2] on the management and care of patients undergoing ophthalmic surgery and briefly outline our standard practice.

At KKESH, as is usual in ophthalmic practice, patients present at the extremes of age, often with diabetes, hypertension, ischaemic heart disease or congenital problems. It is our practice to evaluate fully all of our patients. All patients are subjected to a thorough medical evaluation and appropriate special investigations. Patients considered suitable are encouraged to have their procedures performed under peribulbar anaesthesia, which is our preferred local technique because of its good record. All patients presenting for cataract surgery have axial length determined by ultrasound.

Resuscitation equipment is available in the preoperative holding area and all staff are regularly certified in basic life support. An anaesthetist is always present during performance of blocks. All patients, with the exception of babies and small children, have i.v. access established on arrival in the preoperative holding area. Electrocardiogram and arterial pressure monitoring are started before proceeding with the local block, which is administered by a consultant anaesthetist. Monitoring of electrocardiogram, arterial pressure and oxygen saturation is continued during the procedure by anaesthetic personnel who are present throughout. Patients are returned to the wards when they are considered stable.

A small percentage of peribulbar blocks are performed by ophthalmology registrars under anaesthetic supervision. Registrars are not permitted to administer blocks to patients who have one eye, an axial length longer than 25 mm or staphyloma, or vision in the other eye of less than 20/200; they are not permitted to do "top-ups." Registrars are required to perform 50 peribulbar blocks under supervision during their training. Four of six consultants use 25-mm sharp 25-gauge needles and two use 38-mm sharp 25-gauge needles. All anaesthetists use a standard mixture of lidocaine, bupivacaine and hyaluronidase.

Problems encountered during peribulbar blocks, although uncommon, may be severe and even life threatening, such as central spread of the local anaesthetic agent or activation of the oculocardiac reflex.[3] Patients with treated hypertension or unrecognized labile hypertension may present a problem in the preoperative holding area, particularly after the administration of phenylephrine eye drops

Although we have experience of all of these complications, and even pulmonary oedema, they were always diagnosed promptly and treated immediately. We have never had cause to regret our cautious approach. It has stood the unit in good stead and has resulted in an impeccable anaesthetic outcome. We believe that departure from the above practice represents substandard practice.

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1. Mawer RJ, Coombes AGA. Current practice of local anaesthesia for routine ocular surgery. *British Journal of Anaesthesia* 1998; 80: 241–242.
2. Report of the Joint Working Party on Anaesthesia in Ophthalmic Surgery. London: Royal College of Anaesthetists and Royal College of Ophthalmologists, March 1993.

Editor,—Thank you for the opportunity to respond to Dr Edge and colleagues. The practice at the King Khaled Eye Specialist Hospital (KHESH) appears exemplary. There is no doubt that the Working Party recommendations which they endorse represent very safe anaesthetic practice.

It would be interesting to learn if patients are admitted as day cases, having been assessed only by trainee ophthalmology doctors at a preoperative clinic or whether the anaesthetists have the opportunity to see the patients, either on the ward or in an anaesthetic preclerking clinic before the day of surgery. I am sure this may reflect on what appears to be an ideal preoperative work-up, as yet not always available in the NHS. The training available for inserting peribulbar blocks appears well thought out, yet there is no mention of training for trainee anaesthetists. It is an interesting comparison that in the Kingdom of Saudi Arabia, consultant anaesthetists teach the trainee ophthalmologists, whereas in the UK the reverse is often the case.

The authors failed to quote the rate of complications within the KKESH unit, an omission of which our survey was also guilty, despite quoting the total number of regional blocks given. I find the number of general anaesthetics surprising in view of the apparent quality of the regional block service; does this reflect a large paediatric practice?

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Practical airway assessment

Editor,—Contrary to the conclusions of Arné and colleagues,[1] I believe that multivariate indexes that are designed to help "predict" difficult intubation are of little value to anaesthetists in the real world.

Investigations have focused on the relationship of several factors alone or in combination (e.g. mouth opening, dentition, Mallampati score, neck extension) to the degree of difficulty in seeing the vocal cords with direct laryngoscopy or to "difficulty"[2] associated with actual tracheal intubation. However, I am not aware of any study that has examined the relationship of bedside airway assessment and "difficulty with mask ventilation." What we are really interested in when making clinical decisions is the potential for morbidity (from all possible courses of action) or mortality. A logical analysis predicts that morbidity and mortality result because of difficulty with oxygenation–ventilation, aspiration or trauma related to the chosen method of airway intervention. The ASA airway algorithm[3] implies that unanticipated "difficult airway scenarios" (by whatever definition) will continue to occur despite bedside airway assessment (either because the tests are inherently imperfect[4] and/or because anaesthetists do not know what to do with the information).[4]

It is time we took a more pragmatic approach to bedside airway assessment and airway management until such time that a bedside airway test(s) is developed that can be relied upon to a degree that allows the construction of an algorithm for airway management based on bedside assessment.

I try to teach anaesthesia residents to think of bedside airway management in the following practical terms. First, recognizing that traditional bedside tests are of some, albeit limited, value, I suggest classifying the airway as obviously normal, obviously abnormal or somewhere in between. Then identify any factors that may put the patient at increased risk should there be a brief problem with tracheal intubation (e.g. full stomach, intracranial disease, suspected cervical spine instability, ischaemic heart disease, anterior mediastinal mass, etc.). Consider if there are any alternatives to general anaesthesia or, more specifically, general anaesthesia with a tracheal tube. Recognize that it is extremely unusual to encounter a patient that cannot be ventilated via a face mask (or a laryngeal mask) —although our ability to predict "difficult ventilation with a face mask" remains unquantifiable! Be familiar with the ASA airway algorithm and comfortable with its implementation (which assumes competency with all of its elements) and ensure that the necessary equipment and personnel are immediately available and in "working order". Recognize that techniques designed for the management of the potentially difficult airway are not always benign. Consider giving the patient a choice. Perhaps most importantly, ask yourself what you would want done.

It is time investigators and authors cease to give bedside airway assessment more legitimacy that it deserves! Until someone can show that bedside airway assessment can reliably be used to influence anaesthetists' judgement, airway management will remain a matter of "common sense!"

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1. Arné J, Descoins P, Fusciardi J, Ingrand P, Ferrier B, Boudigues D, Aries J. Preoperative assessment for difficult intubation in general and ENT surgery: predictive value of a clinical multivariate risk index. *British Journal of Anaesthesia* 1998; **80**. 140–146.
2. Adnet F, Borron SW, Racine SW, Clemessy JL, Fournier JL, Plaisance P, Lapandry C. The intubation difficulty scale (IDS). *Anesthesiology* 1997; **87**: 1290–1297.
3. American Society of Anesthesiolgists: Practice guidelines for management of the difficult airway. *Anesthesiology* 1993, **78**: 597–602.
4. Karkouti K, Rose DK, Ferris LE, Wigglesworth DF, Meisami-Fard T, Lee H Inter-observer reliability of ten tests used for predicting difficult tracheal intubation. *Canadian Journal of Anaesthesia* 1996, 43. 554–559.

Editor,—We read with interest Dr Lang's letter regarding the use of predictive scores for preoperative detection of difficult intubation[1] and are grateful for the opportunity to reply.

We agree that the most important problem is to identify "difficulty with mask ventilation" and that the primary goal of bedside evaluation would be to allow construction of an algorithm for airway management. However, as pointed out, the incidence of difficulties in face mask ventilation seems to be very low: El-Ganzouri and colleagues[2] found an incidence of 0.08% in a population of 10 507 patients, and Rose and Cohen[3] found an incidence of 0.01% among 18 500 patients. This low incidence explains why no study to date has determined a bedside multifactorial score of prediction. Inclusion of more than 500 000 patients would be necessary for a multifactorial evaluation. Moreover, construction of such an algorithm must also include situations where difficulties in both ventilation and intubation occur The work of Rose and Cohen[3] failed to identify even one case, despite studying 18 500 patients. Thus a very large epidemiological study, including several million patients, would be required. Bedside prediction of difficult intubation is a more pragmatic approach. If a score predicts difficult intubation with a minimal false negative risk, a positive prediction suggests the patient should be allowed to breath spontaneously thus avoiding potential difficulties with oxygenation and ventilation.

We disagree with the idea that airway management could be only a matter of common sense. In fact, common sense works only when the airway is obviously normal or abnormal. It does not work in intermediate situations, which are the most difficult to predict. The main use of a predictive score is for these intermediate situations where several minor difficulties are associated (e.g. a Mallampati class 2 associated with limitation of neck movement in the 90–100° range). In these cases, using only common sense leads to an erroneous prediction in approximately 50% of patients. When the risk index is applied, the probability of a wrong prediction is reduced to 7%, probably because associated minor signs cannot be missed or forgotten. Dr Lang suggests that sufficient knowledge of an airway algorithm and competency with all the substitutive techniques is more important than an erroneous prediction. We feel that fibreoptic tracheal intubation is easier to perform in spontaneously breathing patients than in apnoeic and paralysed patients. How do you plan spontaneous ventilation without a preoperative prediction?

However, we agree that knowledge of an airway algorithm is always required. The cornerstone of the debate seems to be is it safer to prevent or to treat the problem? Our opinion is that in the field of the difficult airway, as in the more general field of anaesthesia practice, we should prevent and anticipate events rather than treat them

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1. Arné J, Descoins P, Fusciardi J, Ingrand P, Ferrier B, Boudigues D, Aries J. Preoperative assessment for difficult intubation in general and ENT surgery: predictive value of a clinical multivariate risk index. *British Journal of Anaesthesia* 1998; **80**: 140–146.
2. El Ganzouri AR, McCarthy RJ, Tuman KJ, Tanck EN, Ivankovich AD. Preoperative airway assessment: predictive value of a multivariate risk index. *Anesthesia and Analgesia* 1996, **82**: 1197–1204.
3 Rose DK, Cohen MM. The airway: problems and prediction in 18 500 patients. *Canadian Journal of Anaesthesia* 1994; 41: 372–383.

Anaesthetic for telescopic procedures in the thorax

Editor,—I was interested to read the recent review of anaesthesia for telescopic procedures in the thorax, by Plummer, Hartley and Vaughan,[1] but question some of their assertions about oesophagoscopy

First, they state that "a fibreoptic oesophagoscope is generally used for inspection and therapeutic procedures." Most ENT surgeons with whom I have worked use the rigid instrument routinely. Second, their use of reinforced tracheal tubes (presumably those containing a steel spiral within the wall) is at variance with the practice of many anaesthetists, who use pre-formed PVC ("RAE") tubes, and have no problems with tube compression. It is incorrect to assert that "no suitably sized reinforced tracheal tubes [are] available" for use in children, as a full range of such tubes (both paediatric and adult) is available in the UK, manufactured by "Sheridan".

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1. Plummer S, Hartley M, Vaughan RS. Anaesthesia for telescopic procedures in the thorax. *British Journal of Anaesthesia* 1998; **80**: 223–234.

Editor,—We thank Dr Taylor for his remarks and we would like to reply to each in the same order.

First, the word generally does not preclude the use of rigid oesophagoscopy.

Second, we can find no reference to any advantage (or indeed disadvantage) for using the "RAE" tube compared with reinforced tracheal tubes. Until such a positive advantage has been shown I suggest that what has been accepted and is safe practice remains unchanged.

We must apologize for the fact that we were unaware that "Sheridan" produced a full range of adult and paediatric reinforced tubes. However, it would seem logical, given this information, that when any surgical operation around the head and neck is performed, a suitable "Sheridan" reinforced tube is used.

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Appropriate size of the laryngeal mask airway in adults

Editor,—I read with interest the article of Asai and colleagues[1] on the selection of an appropriate size of laryngeal mask airway (LMA). In this study there are some references to my work, as we have some common conclusions.[2] But as there are some misconceptions about our study design, clarification is needed.

Asai and colleagues compared two different sex-related formulae (SRF) for selection of an appropriate size of LMA, but they did not compare their findings with weight-related formulae (WRF).[5,4] The latter have been proposed by the inventor of the LMA and are widely accepted in anaesthesia. In the study of Voyagis, Batzioulis and Secha-Doussaitou,[2] they recommended using size 5 for all males and size 4 for all females, and using a smaller size (No. 4 in males, No. 3 in females) if placement of the LMA was inappropriate. This SRF was compared with the WRF suggested by the inventor in that time period (pre-1996).[3] In our study, the age of the patients was not used as a predictor of LMA size (which was reported incorrectly by Asai and colleagues). When applying the SRF, the use of an LMA No. 5 was eight times more common, as it was used in many non-obese male patients. Mean body weight in these patients was 20 kg lower than that of the control group (SRF: 76 (SD 16) kg *vs* WRF: 96 (6) kg; $P<0.0001$). Brimacombe and colleagues[5] replied to our study by suggesting that further evidence is needed before moving away from weight-based recommendations. However, in October 1996, Brimacombe and Brain[4] revised the quantitative limits of their initial WRF. The new limits are 20 kg lower than the initial ones (i.e. more than 70 kg, size 5; 50–70 kg, size 4; and less than 50 kg, size 3). This new WRF is not significantly different from the SRF suggested previously,[1,2] as the majority of female adults have a body weight of 50–70 kg and the majority of males have a body weight of more than 70 kg.

Although our study is reported by Asai and colleagues as the only one in which an attempt was made to determine the appropriate size of LMA, in the references, the letter of Brimacombe and colleagues[5] is not reported as a reply comment. Additionally, in the introduction, the wrong impression is given that Brimacombe and colleagues recommended the use of an LMA as predicted by gender, but the opposite is true.

Asai and colleagues found that 13% of males (four of 30) and 17% of females (five of 30) had unacceptable security of the airway when LMA No. 5 and No. 4 were used, respectively. Improvement in airtightness was not reported when a smaller size LMA was used in these patients. In our study, the respective frequencies of inappropriate airleak were 16% (11 of 67) in males and 12% (nine of 77) in females, being statistically equal to those of Asai and colleagues. Whenever our patients had unacceptable airleak with the larger sizes of LMA, the use of smaller ones resulted in optimal airtightness.

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1. Asai T, Howell TK, Koga K, Morris S. Appropriate size and inflation of the laryngeal mask airway. *British Journal of Anaesthesia* 1998; **80**: 470–474.
2. Voyagis GS, Batzioulis PG, Secha-Doussaitou PN. Selection of the proper size of laryngeal mask airway in adults. *Anesthesia and Analgesia* 1996; **83**: 663–664.
3. Brimacombe JR, Berry AM, Brain AIJ. The laryngeal mask airway. *Anesthesiology Clinics of North America* 1995, **13**: 411–437.
4. Brimacombe JR, Brain AIJ. Preparation for use. In: Brimacombe JR, Brain AIJ, eds. *The Laryngeal Mask Airway. A Review and Practical Guide.* London: Saunders, 1997; 52–64.
5. Brimacombe JR, Berry AM, Campbell RC, Verghese RC. Selection of the proper size of laryngeal mask airway in adults. *Anesthesia and Analgesia* 1996; **83**: 664.

Editor,—It was my mistake to state that "Voyagis, Batzioulis and Secha-Doussaitou attempted to decide if the patient's *age* or weight was a better indicator for selecting the appropriate size of the laryngeal mask" (italics added)[1]—in fact, they studied the effect of patient sex, not age.[2] However, it should be apparent that my statement was a mistake, since I summarized in the subsequent sentences that they compared sex- and weight-based selection methods.[1]

Dr Voyagis claims that selection of the appropriate size of the laryngeal mask based on the patient's weight is widely accepted in everyday practice, but it may not be so. The majority of anaesthetists I work with decide the size primarily based on the patient's sex. I cited Brimacombe and colleagues' statement that "... based on a common misconception that the size 3 is for females and the size 4 for males" to indicate that it is a common practice among anaesthetists to select the size based on sex; whether or not Brimacombe and colleagues recommend a weight-based selection method is irrelevant here. In fact, I believe that they carefully avoided claiming that size should be selected based on the patient's weight rather than on sex, by stating that "further conclusive trials are required before the manufacturer's weight-based recommendations are altered".[3]

The main purpose of our study[1] was to show that the size 4 is usually not too large to insert in females, and may even be a better choice than the size 3 in terms of incidence of airleak. I did not suggest that an appropriate size of mask should be selected based on the patient's sex rather than on weight. In this respect, I support Brimacombe and colleagues' statement that "judging the correct size of the laryngeal mask can be difficult since the relationship between gender, weight, height and upper airway geometry appears inconsistent".[3]

There are similar difficulties in selecting the appropriate size of a tracheal tube. Nevertheless, the size of a tracheal tube is usually selected based on sex. However, other factors are taken into consideration: patient age, height, weight and size of the skeletal structure, and incidence of complications (such as postoperative sore throat).

I noticed recently that in some apparently large women, the size 5 laryngeal mask provided a better seal than the size 3 or 4 without producing higher pressures on the pharynx, indicating the limitation of the selection of an appropriate size based *solely* on the patient's sex. Therefore, I support fully the claim made by Voyagis, Batzioulis and Secha-Doussaitou[2] that "the overall suggested sex-related formulae do not work in all cases, but might be considered as a general principle".[2] I also believe that neither their[2] or our[1] study contradicts the recommendation in the latest instruction manual that "as large a size of mask as possible should be used".[4]

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1 Asai T, Howell TK, Koga K, Morris S. Appropriate size and inflation of the laryngeal mask airway, *British Journal of Anaesthesia* 1998; **80**: 470–474.
2. Voyagis GS, Batzioulis PG, Secha-Doussaitou PN. Selection of the proper size of laryngeal mask airway in adults. *Anesthesia and Analgesia* 1996; **83**: 663–664.
3 Brimacombe JR, Berry AM, Campbell RC, Verghese C. Selection of the proper size of laryngeal mask airway in adults. *Anesthesia and Analgesia* 1996; **83**: 664.
4. Brimacombe JR, Brain AIJ, Berry AM. *The Laryngeal Mask Airway Instruction Manual.* Intavent Research Limited, 1997, Berkshire, UK.

Editor,—We were interested in the article by Asai and colleagues[1] who assessed the most suitable size of laryngeal mask airway (LMA) by determining the competence of the seal under general anaesthesia. Our attempt, examining instead the incidence of sore throat in 200 patients following the use of a size above and a size below those commonly used, came to a different conclusion.[2]

Frequently used sizes are LMA 4 in men and LMA 3 in women, and we had determined previously the incidence of sore throat using these sizes in a study of 839 patients.[3] Sizes LMA 5 and 3 in men, LMA 4 and 2.5 in women were also tested. A size larger than usual might have been expected to require a lower cuff pressure or alternatively a size smaller might have reduced the surface contact area. The outcome of cuff volume adjustment until leakage of respiratory gases was just prevented was also studied, equivalent to the "just-seal" conditions of Asai and colleagues' fourth group. We found that the incidence of sore throat was significantly lower in men than in women if the cuff was inflated normally, an observation which has been reported elsewhere[4]; it was lower or the same in all patients when the cuff was adjusted to just prevent leakage, and was increased with both the next sizes up (5 and 4, respectively) or the next sizes down (3 and 2.5). In effect, the LMA 4 in men and LMA 3 in women resulted in the lowest incidence of soreness and these would appear to be appropriate sizes.

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1. Asai T, Howell TK, Koga K, Morris S. Appropriate size and inflation of the laryngeal mask airway. *British Journal of Anaesthesia* 1998; **80**: 470–474.
2. Nott MR. A "his" and "hers" laryngeal mask. *Anaesthesia* 1998; **53**: 714–715.
3. Nott MR, Noble PD, Parmar M Reducing the incidence of sore throat with the laryngeal mask airway. *European Journal of Anaesthesiology* 1998; **15**: 153–157.
4. Addy EV, Kapila A, Verghese C. Airway management and the incidence of sore throat. *British Journal of Anaesthesia* 1998; (Suppl. 1). **80**: 19.

Editor,—It may not be surprising that Drs Nott and Hill reached a different conclusion from us as they looked at different end-points from ours to decide an appropriate size of laryngeal mask. They made their decision based on the incidence of postoperative sore throat,[1,2] whereas we did so mainly on the incidence of airleak during manual ventilation.[3] Despite a difference in *conclusion*, I believe that their results[1,2] and ours[3] are generally consistent.

First, in Drs Nott and Hill's studies,[1,2] when the cuff volume of the laryngeal mask was not adjusted (i.e. the mask being inflated with the recommended maximum volume of air), the incidence of sore throat was higher when a larger (size 4 in females and size 5 in males) than a smaller (size 3 in females and size 4 in males) mask was used. Similarly, in our study,[3] when the mask was inflated maximally, the pressure exerted on the pharynx was greater with a larger than with a smaller mask.

Second, they found that the incidence of postoperative sore throat was reduced by adjusting the cuff volume of the laryngeal mask to the minimum effective volume ("just-seal" condition).[1,2] These results are consistent with ours[3]: removal of air from the maximally inflated cuff to the minimum effective volume significantly decreased the pressure exerted by the mask on the pharynx.

Third, in their study, when air was removed from the mask to the effective minimum volume, there was no marked difference in the incidence of sore throat between sizes 4 and 5 in males.[1,2] This is also consistent with our findings that there was no significant difference between the pharyngeal pressures produced by the two sizes in males [3]

The last finding of Drs Nott and Hill, however, is apparently not consistent with ours: they claimed that the incidence of sore throat associated with the use of the size 4 was greater (approximately 20%) than that for the size 3 (they report 3.9%, but it is in fact 7.3% (16 of 219 patients)) in females.[1,2] In contrast, in our study, there was no significant difference in pharyngeal pressure between sizes 3 and 4.[3] There are two possible explanations for this inconsistency. First, the difference in the incidence of postoperative sore throat in their report might not be significant if a statistical analysis was applied for this difference, although there is difficulty in doing so as historical controls were used.[1,2] The second possibility is that size 4 causes a higher incidence of sore throat than size 3, by producing abrasion of a wider area of the oropharynx during insertion

Taken together, I believe that the following two conclusions can be drawn from Drs Nott and Hill's study and ours First, the pressure exerted by the laryngeal mask on the pharynx and incidence of postoperative sore throat can be reduced by removing air from the maximally inflated cuff to the minimum effective volume (or "just-seal" condition). Second, intracuff pressure, the pressure exerted on the pharynx and the incidence of postoperative sore throat are greatest when a large laryngeal mask is used without adjusting cuff volume, therefore, cuff volume should be adjusted to the minimum effective volume, particularly when a large mask is used.

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1. Nott MR, Noble PD, Parmer M. Reducing the incidence of sore throat with the laryngeal mask airway *European Journal of Anaesthesiology* 1998; **15**: 153–157.
2. Nott MR A "his" and "hers" laryngeal mask? *Anaesthesia* 1998; **53**: 714–715.
3. Asai T, Howell TK, Koga K, Morris S. Appropriate size and inflation of the laryngeal mask airway. *British Journal of Anaesthesia* 1998; **80**: 470–474.

Paddle size in defibrillation

Editor,—The success of defibrillation is determined by transmyocardial current which comprises a proportion of the total transthoracic current. Transthoracic current is inversely proportional to transthoracic impedance (TTI). Low TTI has therefore been equated with generating higher transmyocardial current, and by implication, improved success from defibrillation. For example, the low TTI achieved when using adult defibrillation paddles on children has been assumed to improve outcome from defibrillation.[1]

Although a decrease in TTI increases overall transthoracic current, it does not necessarily increase total transmyocardial current. Above an optimal paddle size, some current traverses extracardiac pathways through the thorax, bypassing the heart,[2] and results in reduced transmyocardial current. This has been demonstrated in canine studies in which larger paddles reduced TTI but greatly reduced defibrillation success rate (33% *vs* 83%).[2,3] Failure to improve transmyocardial current with increasing paddle size may also explain why some studies have failed to show any benefit in cardioversion success rates using larger paddles.[4,5] Therefore, measurement of TTI alone cannot establish if paddle size is optimal

Current guidelines quoting 13 cm as the optimum paddle size in adults[6] are not based on studies of transmyocardial current or defibrillation success at different pad sizes. Since optimum paddle size in dogs is approximately 13.0 cm and canine hearts are smaller than human hearts, it has been suggested that optimum size in humans may actually be larger than 13 cm.[3,7] The optimum paddle size in humans remains to be determined.

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1. Atkins D, Sirna S, Kieso R, Charbonnier F, Kerber R. Pediatric defibrillation· importance of paddle size in determining transthoracic impedance. *Pediatrics* 1988; **82**· 914–918.
2 Ewy G. Effectiveness of direct current defibrillation: role of paddle electrode size II. *American Heart Journal* 1977, **93**. 674–675
3. Thomas E, Ewy G, Dahl C, Ewy M. Effectiveness of direct current defibrillation· role of paddle electrode size. *American Heart Journal* 1977. **93**: 463–467.

4. Kerber R, Jensen S, Grayzel J, Kennedy J, Hoyt R. Effective cardioversion: influence of paddle–electrode location and size on success rates and energy requirements. *New England Journal of Medicine* 1981; **305**: 658–662.
5. Hoyt R, Grayzel J, Kerber R. Determinants of intracardiac current in defibrillation. Experimental studies in dogs. *Circulation* 1981; **64**: 818–823.
6. Bossaert L. Fibrillation and defibrillation of the heart. *British Journal of Anaesthesia* 1997; **79**: 203–213.
7. Hoyt R, Grayzel J, Kerber R. Intracardiac current in defibrillation. Effect of paddle size. *Circulation* 1979; **59** (Suppl II): II–192.

Editor,—The point made by Dr Deakin is correct. As with many other aspects of resuscitation, practice is guided by convention, tradition and extrapolation from animal experience, but scientific evidence is missing. This applies to electrode size: optimal electrode size in humans has still to be determined. Many of the investigations are limited to studying paddles of manual defibrillators, but the problem is at least as important for self-adhesive electrodes of automated external defibrillators.

Although sudden cardiac death from ventricular fibrillation is the single most frequent cause of death in the industrialized world and defibrillation is recognized as the only effective treatment for ventricular fibrillation, our knowledge and understanding of the mechanisms of defibrillation in humans are still limited. It is well known that the effect of defibrillation is very much dependent on the various technical characteristics of the components of the "defibrillator–paddles–couplant–chest complex". Little scientific evidence is available on the absolute and time-dependent influence of these various components on transthoracic impedance, transthoracic and transmyocardial current or the influence of paddle size, shape and couplant on the characteristics and duration of the behaviour of the electrocardiographic surface signal immediately after delivery of an electric shock. Little scientific evidence is available relating to the optimal energy of the first and subsequent shocks, the optimal waveform for defibrillation or optimal electrode size and shape.

Since the introduction of automated external defibrillators, using self-adhesive pads, interest in optimal technology, including electrode technology, has increased suddenly. Resuscitation councils such as the European Resuscitation Council have repeatedly insisted on the need for standardization for electrodes and connectors for automated external defibrillators.[1] This plea for standardization could be an incentive for the defibrillator industry to focus their research on these aspects and to share their knowledge and research programmes with the clinical investigators.

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1. Bossaert L, Handley A, Marsden A, Arntz R, Chamberlain D, Ekström L, Evans T, Monsieurs K, Robertson C, Steen P. European Resuscitation Council guidelines for the use of automated external defibrillators by EMS providers and first responders. *Resuscitation* 1998; **37**: 91–94.

An extrapyramidal reaction to ondansetron

Editor,—A healthy, 37-yr-old female presented for evacuation of retained products of conception after intrauterine death at 18 weeks' gestation. She gave a history of severe postoperative nausea and vomiting, which had previously been treated successfully with metoclopramide. Therefore, it was decided to administer ondansetron 4 mg i.v. before induction of anaesthesia.

A few minutes after administration of ondansetron, she began to complain of blurred vision and dizziness. Induction was continued and, after pre-oxygenation, rapid sequence induction was performed with thiopental 375 mg and succinylcholine 75 mg followed by tracheal intubation. Anaesthesia was maintained with 1.2% inspired isoflurane and 70% nitrous oxide in oxygen, and supplemented with alfentanyl 500 µg, with the patient breathing spontaneously.

Recovery after the procedure was punctuated by a brief episode of larygospasm on extubation, but was otherwise uneventful and rapid. The patient had no postoperative nausea or vomiting and experienced very little pain. However, she complained of blurred vision and had uncontrollable movements of her eyes, face and arms. On examination, she had marked horizontal nystagmus, involuntary eye movements and mild choreiform movements of her arms. She was observed for 30 min, during which time there was no improvement in her symptoms. She was given procyclidine 5 mg i.v. and her symptoms stabilized within 5 min. She was observed for 2 h during which time there were no further episodes. She was transferred to the ward where the rest of her recovery was uneventful.

Extrapyramidal reactions to ondansetron have been reported[1–4] when ondansetron has been used in higher and repeated doses of 8–30 mg 8-hourly, for prevention of nausea and vomiting during chemotherapy. As far as I am aware, extrapyramidal reactions to ondansetron have not been reported in the anaesthetic literature. This case suggests extrapyramidal reactions may be caused after a single, small i.v. dose of ondansetron.

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1. Garcia-del-Muro X, Cardenal F, Ferrer P. Extrapyramidal reaction associated with ondansetron. *European Journal of Cancer* 1993; **29A**: 288.
2. Dawn Camp-Sorrel. Managing an extrapyramidal reaction caused by ondansetron. *Oncology Nursing Forum* 1995; **22**: 718–719.
3. Matthews HG III, Tancil CG. Extrapyramidal reaction caused by ondansetron. *Annals of Pharmacology* 1996; **30**: 196.
4. Kristenansky PM, Petree J, Long G. Extrapyramidal reaction caused by ondansetron. *Annals of Pharmacotherapy* 1994; **28**: 280.

Postdural puncture headache after combined spinal–epidural analgesia and anaesthesia

Editor,—Combined spinal–epidural (CSE) analgesia[1] has become increasingly popular for analgesia in labour. However, several authors have questioned the desirability of routine dural puncture. Among other criticisms of the technique it has been suggested that CSE analgesia is associated with a greater risk of post-dural puncture headache (PDPH) than epidural analgesia.[2]

We have examined retrospectively the reported incidence of headaches in 2086 consecutive obstetric patients after epidural block, subarachnoid block or CSE These were performed for elective Caesarean section ("elective" CS), in labour for analgesia or for emergency CS ("emergency"). The reported incidence of headache after receiving regional analgesia or anaesthesia is shown in table 1.

Table 1 Reported headache rate in women after regional analgesia or anaesthesia. *This patient received a dural puncture with a 20-gauge spinal introducer needle

Procedure		Total	No. of women reporting headaches	Obvious dural puncture
Epidural (16-gauge Tuohy)	Elective	13	0	0
	Emergency	1219	21 (1.7%)	5 (0.4%)
Subarachnoid (25-gauge polymedic)	Elective	107	0	0
	Emergency	112	0	1 (0.9%)*
CSE (25-gauge through 16-gauge Tuohy)	Elective	246	1 (0.4%)	2 (0.8%)
	Emergency	389	10 (2.6%)	5 (1.3%)

Of the small number of patients receiving elective epidural anaesthesia, none complained of headaches. Of the 1219 patients receiving epidural analgesia–anaesthesia in labour, 21 complained of a headache after delivery. Only five (0.4%) of these had identified dural punctures. All others were complaints of minor headaches not typical of PDPH which resolved with simple analgesia or no treatment.

Of the group of patients receiving subarachnoid analgesia, none of the elective or emergency patients complained of headaches, despite one of the patients having a dural puncture from the 20-gauge spinal introducer needle.

Of the 635 patients receiving CSE, 246 had an elective procedure for a planned LSCS; two (0.8%) of these patients had an identified dural puncture with a 16-gauge Tuohy needle. Only one of these complained of a headache and required an extradural blood patch for treatment. A total of 389 patients received CSE for analgesia in labour or for emergency LSCS. Ten (2.6%) of these patients complained of headache, five (1.3%) of whom had identified dural punctures with a 16-gauge Tuohy needle; four of these required an epidural blood patch to alleviate the PDPH. The others had minor headaches not typical of PDPH, all of which resolved after treatment with simple analgesia.

These data would support the hypothesis that CSE analgesia is not associated with a clinically significant increased incidence of severe headache. The majority of severe headaches in our audit were caused by dural puncture with the Tuohy needle in emergency cases. This is probably a reflection of our practice of performing CSE analgesia in women who are in severe pain in late labour or before emergency Caesarean section because of the previously reported advantages of speed of onset and better sacral dermatomal analgesia.[3]

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1. Collis RE, Baxandall ML, Srikantharajah ID, Edge GE, Kadim KY, Morgan BM. Combined spinal extradural analgesia: technique, management and outcome of 300 mothers. *International Journal of Obstetric Anesthesia* 1994; **3**: 75–81.
2. Jenkins JG. Ambulatory extradural analgesia in labour and mode of delivery. *British Journal of Anaesthesia* 1997; **78**: 776–777.
3. Stacey RGW, Watt S, Kadim MY, Morgan BM. Single space combined spinal–extradural technique for analgesia in late labour. *British Journal of Anaesthesia* 1993; **71**: 499–502.

Pharmacokinetics of propofol during conscious sedation using target-controlled infusion

Editor,—I read with interest the study by Oei-Lim and colleagues regarding the use of target-controlled infusions.[1] The authors stated that "after approximately 60 min of infusion time, the model tended rather to under predict the measured concentration than vice versa". The authors also provided a concentration–time profile (fig. 6) to support their statement. The first three measured concentrations on this figure appear to be increasing, after which the measured concentrations appear to form a plateau. This same trend is seen with the profile predicted using Gepts' model, although the predicted concentrations were much higher than the measured concentrations. However, concentrations predicted by the pharmacokinetic optimization (PKOPT) program appear to be on an upward trend throughout the duration of the infusion.

This suggests that contrary to what was stated by the authors, Gepts' model appears to be consistently over predicting the measured concentrations. This has previously been observed when using propofol in a target-controlled infusion in neurosurgical patients.[2]

The same may not apply to the PKOPT model as the over prediction appears to be increasing progressively with time. This suggests that if a constant plasma concentration is targeted, the measured concentration decreases with time leading to the risk of the patient being in a lighter level of anaesthesia. Some measure of the change of performance with time such as "wobble" or "divergence" might be useful to further describe the performance of the infusion system.[3,4]

Furthermore, clearance calculated using Gepts' model (28.7 litre min^{-1}) is similar to the clearance calculated using the PKOPT model (29.0 litre min^{-1}). This means that at steady state, when the concentration is determined only by infusion rate and clearance, both models predict similar blood propofol concentrations. If Gepts' model tends to under predict the measured concentration during long infusions, the performance of the PKOPT model will be equally poor in a similar situation.

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1. Oei-Lim VLB, White M, Kalkman CJ, Engbers FHM, Makkes PC, Ooms WG. Pharmacokinetics of propofol during conscious sedation using target-controlled infusion in anxious patients undergoing dental treatment. *British Journal of Anaesthesia* 1998; **80**: 324–331.
2. Lim TA, Gin T, Tam YH, Aun CST, Short TG. Computer controlled infusion of propofol for neurosurgical procedures. *Journal of Neurosurgical Anesthesiology* 1997; **9**: 242–249.
3. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. *Journal of Pharmacokinetics and Biopharmaceutics* 1992; **20**: 63–94.
4. Short TG, Lim TA, Tam YH. Prospective evaluation of pharmacokinetic model controlled infusion of propofol in adult patients. *British Journal of Anaesthesia* 1996; **76**: 313–315.

Editor,—Thank you for the opportunity of responding to Dr Lim's letter regarding our article on the pharmacokinetics of propofol during dental sedation.

His comments relate to paragraph 4 of the discussion section. At the end of his letter, Dr Lim states that clearance in Gepts' model (28.7 litre min^{-1}) in the original delivery system used to deliver propofol to our dental patients was almost exactly the same as that of the PKOPT model (29.0 litre min^{-1}) derived in our study to optimize propofol delivery. First, the units of clearance quoted are incorrect. The correct units are ml min^{-1} kg^{-1}. The clearance values calculated by Lim for the Gepts and PKOPT models arise unfortunately from three typing errors in table 2; the units of V_c are given incorrectly as litres whereas the correct units are ml kg^{-1}, second, the value of V_c in the PKOT model should be 417 ml kg^{-1} (rather than 471 ml kg^{-1} which appears in the table) and third, the value of K_{12} for the PKOPT model should be 0 144 rather than 0.114 min^{-1}. Consequently, this means that the calculated clearance for the PKOPT model is 25.64 ml kg^{-1} min^{-1} and that for the Gepts' model is 28.7 ml kg^{-1} min^{-1}. We apologize for these errors which arose in the publishing process but were not subsequently detected when we read the proofs.

Because the clearance values of the two models are similar, the two models will, as Dr Lim states, ultimately predict similar concentrations at steady state when the peripheral compartments are equilibrated with the central compartment of the models. However, for propofol, this steady state situation takes approximately 6 h to attain. In the first part of our study, the procedures were completed within 2 h and we therefore suggest that Dr Lim's remarks concerning steady state are not relevant to our study.

Notwithstanding the above-mentioned errors, the simulation in figure 6 is correct. During the first 60 min of infusion, there was a substantial difference in propofol concentrations predicted by the two models and we have shown that the PKOPT model optimally described the observed data compared with the original model of Gepts, which systematically over predicted the observed data. We confirmed this finding in our prospective study. The simulation we have performed in figure 6 demonstrates that, according to the PKOPT model 1 (which optimally described the population data that we obtained in our study), the Gepts' model, when used as the delivery model in a TCI system, resulted in a steadily increasing plasma concentration of propofol and, presumably, a deepening level of sedation during the time span of our study. When the PKOPT model parameters were used to deliver propofol in a modified TCI delivery system, an improved model performance was obtained.

It should be borne in mind that both the Gepts' and PKOPT models are "averaged" population models. The performance of each model will vary from patient to patient and also for each individual with time. The performance of a given model for an individual patient is relatively unimportant in relation to how the population *as a whole* behaves. In figure 6, the data points from an individual patient were over predicted by both models. However, the prediction error was less for the PKOPT than for Gepts' model. It was not stated that the patient was a "best fit" for the PKOPT model. In this graph, for this particular individual, the PKOPT model described the data better than Gept's model. The PKOPT model described the *population* optimally but not necessarily any one *individual*.

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British Journal of Anaesthesia 1998; 81: 660–661

BOOK REVIEWS

Anesthesiology Pocket Guide. T. N. Pajewski. Published by Lippincott-Raven, Philadelphia. Pp. 465; indexed; illustrated. Price US $34.50.

This compact handbook is designed for use in those clinical situations when a specific fact relevant to anaesthetic practice is required, but a larger reference text is not readily available. Its small size means that it fits into the pocket of theatre clothing and is easily accessible. The information is presented as a series of tables, lists, illustrations, definitions and emergency algorithms. This information is divided into the major chapter headings of preoperative assessment, pharmacology, physiology, regional anaesthesia, paediatric anaesthesia, obstetric anaesthesia and pain management. The final section contains protocols published by the American Society of Anesthesiologists on standards of patient care. Also included are the Advanced Cardiac Life Support (ACLS) protocols. The majority of the information has been reproduced from textbooks and journals but there are many tables which the author has compiled himself. Although there is rarely any explanatory text with the information, there is a comprehensive list of references should further detail be required. The topics covered in this book are extremely wide ranging and the information is often very detailed. With handbooks of this type, it is difficult to decide which facts should be included and which left out. Within the confines of a pocket-sized book, it is inevitable that some subjects will be covered better than others. This book is no exception.

The weakest chapter in the book is that covering preoperative assessment of the patient undergoing anaesthesia. There is much detail about the assessment of the cardiovascular system, including several pages on artificial pacemakers, yet there is little mention of, for example, investigation of patients with chronic respiratory, renal, endocrine or neurological disease. Aspects of these topics are covered in the physiology chapter but would perhaps have been better collected under the same heading of preoperative assessment.

The pharmacology chapter is detailed and comprehensive, covering all of the commonly used agents and some which are used rarely. Most of the new agents are included, with the notable exceptions of remifentanil and ropivacaine. Details on obsolete drugs such as Althesin, methoxyflurane and propanidid are interesting but should be omitted in a book where space is limited. There are conversion tables for calculating infusion rates but many of the dilutions quoted for drug infusions are markedly different from those used in British anaesthetic practice, limiting the usefulness of this section to British anaesthetists. Also, there are clear errors in the doses quoted for some drugs, in particular in the section on neuromuscular blocking agents. The infusion rate for atracurium is stated to be 5–9 mg kg^{-1} min^{-1}; this is clearly a massive overdose and must be a typographical error.

But several of the chapters are excellent. Those on obstetric anaesthesia, paediatric anaesthesia and pain management contain large amounts of information which would otherwise take some time to retrieve from more weighty tomes. The paediatric chapter contains a list of syndromes and details their clinical features; this would normally be found only in a specialist paediatric text. There are many other examples of useful tables such as that which describes the management of severe pre-eclampsia and eclampsia.

In summary, I think that this is a good book. It may require editing in future editions so that some of the information is discarded in favour of more clinically useful material The page devoted to the intricacies of operating room lasers, for example, could easily be replaced by one covering the management of the diabetic patient. Also, a chapter on intensive care would be a useful addition. However, Dr Pajewski has done an admirable job in producing an easy to use book which will find its way into the back pocket or briefcase of many anaesthetists.

M. R. Goulden

Simulators in Anesthesiology Education. L. C. Henson and A. C. Lee (editors). Published by Plenum Publishing Corporation, New York. Pp. 124; indexed; illustrated. Price US $65.

For anyone interested in teaching or already working with simulators, this book is one to have. It is a highly informative text, bringing together a collection of presentations at the Second Annual Conference on Simulators in Anesthesiology Education in Rochester, New York, in 1996. The editors have achieved what they set out to do, which was "to present work done over the previous few years with simulators in the field of anesthesiology education".

The chapters are written by many of the leaders in this field of education, not just physicians but nurses, technicians and educators who use simulators. I believe this is one of the strengths of the book as it shows the wider application of simulators for education. For anyone beginning work in this field, it is this cross-fertilization of educational ideas that enables the teachers to use simulators effectively but also identifies the potential audiences, and therefore income, related to this form of education.

Anaesthetic simulators are a relatively new concept. Both the mechanical engineering and computer modelling that are involved in high-fidelity simulators are continually being developed to improve the realism of the systems. Vimal Chopra's chapter entitled "What can you do with a simulator?" includes a useful guide to the terminology, categorization and description of many of the different simulators being used around the globe. The chapters by van Meurs (Model driven simulators from the clinical instructor's perspective) and Stern (Technical workshop: mathematical and computer models) are perhaps too detailed for the general reader. However, both chapters provide useful technical background information for those beginning to use high-fidelity simulators or wishing to evaluate the different systems available.

I should point out that all the contributions to this book were made in 1996 and the mechanical aspects and computer modelling that make up the high-fidelity simulators are changing rapidly to improve the realism of these systems. I also suspect that all of the contributors would have more to say on the educational and research issues addressed in this book. This is a fast moving field.

Although there are only two high-fidelity simulators in the UK, there is increasing curiosity about the use of simulators for medical education. For those involved in assessing the educational value and cost of purchasing and running a simulator, this book has some useful information. In particular, Zimmerman outlines many of the issues relating to those starting a simulator programme and these issues relate equally well to those setting up a low-fidelity system such as ACCESS or a high-fidelity commercial human patient simulator.

As a simulator user I have come away from reading this book with a number of new ideas to try. Descriptions of the ways in which simulators are used to teach high school students, nursing and resident programmes may bear resemblance to some of the work being done by the low- and high-fidelity simulator user groups in the UK already, but provide a slightly different perspective. It is hard to imagine that this book will ever find a huge audience because it is of such specialist interest. However, I would highly recommend it to anyone interested in medical education with or without the aid of simulators!

F. C. Forrest

International Anesthesiology Clinics. Management of the Operating Room, Vol. 36. M. Wilcock (editor). Published by Lippincott-Raven, Philadelphia. Pp. 108; indexed; illustrated. Price US $57.

A list of the major problems besetting operating departments in the NHS would include: recruitment, training and retention of skilled staff; over-running or under usage and cancellation of booked lists, in large part a reflection of the tradition of "ownership" of operating sessions by surgeons; funding the update and replacement of equipment; managing the interface between staff of different training backgrounds, nursing, technician and ODP, providing structures that reflect this variety and offer career opportunities to all; accommodation of emergency work without disruption of planned lists; difficulties in inter-personal relationships between theatre staff and theatre users; and achieving economy and efficiency in supplies management.

This book consists of nine chapters written by authors from the USA dealing with the apparently rather different spectrum of issues confronting their operating rooms. There are, of course, shared problems, and the more entrepreneurial aspects of some of the discussions in this book might alter the thinking of clinicians in the UK. Several chapters emphasize the message that the operating department should be regarded as a tool whereby the health care organization (in our situation a hospital trust or purchasing/commissioning authority) achieves its objectives This implies both that decisions regarding theatre development should be driven by the ambitions of this greater organization rather than those of surgeons, anaesthetists or theatre management, a concept still novel in the NHS, and that the health care organization has clear and explicit ambitions with a strategy for achieving them.

One chapter deals in rather general and simplistic terms with the role of a medical (clinical) director and another, on the Association of Operating Room Nurses, written by its president, describes its educational and certification activities, sometimes using laudatory language which suggests, rightly or wrongly, that this organization has not acquired the pre-eminence that the author believes it ought A chapter presents a glossary of a comprehensive, not to say awe-inspiring, list of "procedural times", introduced in an attempt to achieve standardization of terminology between institutions. The problem addressed is familiar to anyone who has implemented a theatre computer system but the chapter is not a good read.

A chapter on management concepts is a wide-ranging review of the responsibilities of and skills required for successful operating department management, and one on financial and material management is a combination of useful information, suggestions and concepts for the novice or would-be manager, together with opaque formulae, calculations and charts to which only passing reference is made in the text. Emphasis is placed on the easily forgotten costs of storage and order processing. Other chapters highlight the increasing pressure to control anaesthetic costs and discuss US regulatory and legal issues, together with some aspects of hazard avoidance. One proposes that the key to quality improvement is a clinical/administrative debriefing regarding each patient, followed by multidisciplinary analysis of the data, and presents sample criterion documentation for this. The final chapter occupies almost one-fifth of the volume. It describes the purposes, both individual and corporate, of performance appraisal, emphasizing the need for objective, documented and defensible appraisal systems. It includes a volume of detail, jargon and legislative information, meaningful to few clinicians and out of sync with the overview style that characterizes the rest of the edition.

The book, as always in this series, is well produced and pleasant to handle. It will widen the understanding and appreciation by readers of the broader environment in which we all work.

M. Cohen

Principles and Practice of Total Intravenous Anaesthesia. I. SMITH AND P. F. WHITE. Published by BMJ Publishing Group, London. Pp. 153; indexed; illustrated.

This book is part of the *Principles and Practice* series and as such is designed as an introduction to total i.v. anaesthesia (TIVA) rather than as a reference textbook. It consists of six chapters covering historical aspects, i.v. drug pharmacology, delivery systems, advantages and disadvantages of TIVA, application of TIVA to special patient groups and future developments. The introductory chapter details briefly the historical development of i.v anaesthesia dating from the first i.v. injections in the 17th century up to current practice. A brief introduction to basic pharmacokinetics and pharmacodynamic principles is included in this opening chapter The second chapter covers the different types of i.v. anaesthesia and details the development of TIVA from techniques such as neurolept anaesthesia. This is perhaps the weakest chapter in the book; the contents could have been usefully compressed and included in the introduction.

Pharmacokinetics and pharmacodynamics of individual drugs are considered in the third chapter. Newer drugs such as remifentanil are included, in addition to drugs of historical interest, such as Althesin. Drugs used as adjuvants to anaesthetics are also included, and neuromuscular blocking agents. The latter arguably could have been excluded as most basic anaesthetic texts contain as much if not more information on this group of agents.

The use of i.v. anaesthesia in special patient groups is covered with reference to day-case procedures, paediatrics, the elderly and the critically ill. The differences in dose requirements are explored in these specific populations, emphasizing the pharmacokinetic–dynamic factors responsible for these differences.

I.v. drug delivery is documented in a logical and progressive manner starting with simple i.v. bolus techniques through to computer-controlled delivery and closed-loop control anaesthesia The section on monitoring is informative and interesting but its inclusion in the text tends to suggest that some form of EEG monitoring is required or desirable when using TIVA rather than inhalation agents, which is clearly not the case. The penultimate chapter deals with the advantages and disadvantages of TIVA, toxic effects of volatile agents are detailed together with outcome studies examining recovery and complications after anaesthesia. Finally, a brief summary of future developments is given.

All in all, this book is a good general introduction to i.v. anaesthesia for the trainee. It introduces modern concepts in pharmacokinetics such as context-sensitive half-life and effect site concentration, although these are not always followed through into subsequent chapters, where only the standard pharmacokinetic variables for many of the drugs are discussed. Much more useful information could have been given for example by including the $T_{\frac{1}{2}}K_{\infty}$ for each agent rather than the K_{∞} for just some of the anaesthetic agents, with a clear explanation of how to use such information in daily practice.

There are several small errors in the book. Page 14, line 9, states "A microrate constant describing the transfer of drug out of the central compartment into the *central* compartment can be defined" should read; "A microrate constant describing the transfer of drug out of the central compartment into the *effect site* compartment can be defined". This may cause confusion to readers not familiar with the concept. A large portion of the data in the graph on page 135 appears at first sight to be missing, and it is only clear why this is so by reference to the main body of the text.

These small criticisms aside, the book is a concise account of the basics of i.v. anaesthesia and can be recommended to those seeking to familiarize themselves with the principles of the technique

N. Sutcliffe

ERRATA

Haemodynamic effects of Org 9487 in patients undergoing coronary artery surgery. (BJA 1998; 81: 282–283. Anaesthetic Research Society Abstracts).

Two errors occurred in table 8 of this abstract. Heart rate for Org 9487 at 5 min was incorrectly published at 5 beat min^{-1}. The correct value should be 58 beat min^{-1}. Also, the units for SVR were incorrectly published as dyne s^{-1} cm^{-5}. The correct units are dyn s cm^{-5}.

Effect of l-lysine on nitric oxide production in ovine endotoxaemia. (BJA 1998; 81: 188–192).

Throughout this article, the units for SVR were incorrectly published as dyn s^{-1} cm^{-5}. The correct units are dyn s cm^{-5}.

We apologize to the authors for these errors, which arose during the editorial process.

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

Improved performance with single dose phosphodiesterase inhibitor?

An increasing proportion of patients presenting for anaesthesia and surgery have a degree of myocardial ischaemia and failure. This is especially true in patients with "end-stage" heart disease, that is those patients who require heart surgery. Advances in angioplasty and medical management have increasingly led to a patient population undergoing cardiac surgical procedures that is older, has worse preoperative myocardial function and is more likely to suffer coexisting disease processes.

Factors associated with an increased likelihood of a need for inotropic support to facilitate weaning from cardiopulmonary bypass (CPB) include increasing age, low preoperative ejection fraction, cardiac enlargement and a high baseline left ventricular end-diastolic pressure on ventriculogram.[1 2] In addition, there are several clinical scenarios related to vascular, orthopaedic and general surgery where these patients have a degree of added myocardial depression at the end of surgery. This may require short-term support to maintain an appropriate cardiac output.

In patients undergoing heart surgery before attempts at separation from bypass, there are known risks and benefits of providing early inotropic intervention, which are listed in table 1.

Thus the ideal drug for *prophylactic* use in patients deemed to be at high risk of requiring inotropic support would improve haemodynamic variables with minimal side effects, especially in those who may require support for only a short time.

There is no ideal inotrope available at present. Inotropic drugs used for separation from CPB include β-agonists and phosphodiesterase inhibitors (PDE). Both groups of agents have advantages and disadvantages. The effectiveness of β-adrenergic drugs in the situation of a failing myocardium after bypass is limited by side effects such as arrhythmia, increased myocardial oxygen consumption and peripheral vasoconstriction. Beta receptor desensitization may also lead to the development of tolerance and thus limit the usefulness of catecholamines. Administration of epinephrine (adrenaline) may be associated with increased myocardial ischaemia and an increase in diastolic filling pressures. Patients who are receiving inotropic support after bypass have a higher incidence of arrhythmia and are more tachycardic, a major risk factor for increasing ischaemia, when receiving β-agonists. All β-agonists have a very short half-life and must be administered as a continuous infusion. This allows rapid titration to effect, but can be time consuming to prepare and may require frequent adjustments in infusion rate.

Table 1 Risks and benefits of early inotropic intervention during cardiac bypass surgery

Risk/disadvantage	Benefit/advantage
Unnecessary drug use	Increased myocardial contractility
Tachycardia/arrhythmia	Resolution or prevention of ischaemia
Hyper/hypotension	Simplified control of possible side effects of inotropic agents while on bypass
Possible myocardial damage	Dilation of the internal mammary artery
Need for other agents to treat the side effects of the inotropes	Prevention of the "failed wean" and its attendant complications

Phosphodiesterase inhibitors such as amrinone, milrinone and enoximone differ in their presentation and physical properties (table 2). All display positive inotropic activity based on inhibition of phosphodiesterase type III (PDE III), which results in increased concentrations of cAMP. They also induce an increase in calcium sensitivity at the sarcoplasmic reticulum. These two mechanisms lead to improvement in myocardial contractility. These performance-enhancing effects on the muscle are complemented by other actions caused by inhibition of other phosphodiesterase isoforms, leading to an increase in cyclic GMP. The effect of this is to cause vasodilatation to improve diastolic compliance, reduce afterload and prevent internal mammary artery spasm.[3] As the PDE III inhibitors bypass β-adrenergic receptors to increase cAMP, they potentiate the effects of ß-agonists thereby allowing reduction in the requirements for those agents.[4 5] Also, they do not cause significant tachycardia and are considerably less arrhythmogenic than sympathomimetic drugs.

On pharmacodynamic criteria, the PDE III inhibitors seem to have a better profile than β-agonists. The question therefore is to determine the most appropriate patient, time and dose regimen for administration of a PDE III inhibitor.

PDE III inhibitors have been studied in the context of: (a) patients with cardiac failure who have not undergone surgery; (b) those who have developed low output failure after bypass, either after a failed weaning attempt or subsequently on the intensive care unit[5–9]; and (c) patients who were thought to be at risk during weaning and therefore were given prophylactic PDE III inhibitor into the pump.[6–14]

All of these reports demonstrated a consistent increase in cardiac index, with a decrease in systemic and pulmonary vascular resistance. Dose requirements in surgical compared with medical patients have been shown to be less, presumably because of differences in the underlying pathophysiology of heart failure. The therapeutic response to milrinone was shown in the European multicentre study[6] to be partially determined by pretreatment haemodynamics; the greatest proportional response in cardiac

Table 2 Characteristics of the three phosphodiesterase III inhibitors available for therapeutic use. All agents are given i.v. but have marked differences between physical and pharmacological characteristics

	Amrinone	Milrinone	Enoximone
Availability	Not in UK	Europe, USA, Australia, New Zealand	UK, Netherlands, Germany, Ireland and Belgium but not USA
Loading dose			
Cardiac failure	0.75 mg kg^{-1} over 2–3 min	50–75 μg kg^{-1}	0.5–2.0 mg kg^{-1}
CPB	1.5–2.0 mg kg^{-1} into CPB system	50 μg kg^{-1} into CPB system	0.5–1.0 mg kg^{-1} into CPB system
Infusion rate	5 μg kg^{-1}min^{-1} maximum 20 μg kg^{-1} min^{-1} post-CPB	0.25–1 μg kg^{-1} min^{-1} 0.375–0.75 μg kg^{-1} min^{-1} post-CPB	0.75 mg kg^{-1} h^{-1} or 2–20 μg kg^{-1} min^{-1}
Storage	Room temperature Protect from light	Room temperature	≤20°C (usually in refrigerator)
Diluent	0.9% or 0.45% sodium chloride Inactivated by dextrose diluent but can be given in same line as dextrose infusion	Stable in all dextrose and sodium chloride solutions	Must be diluted before administration Diluent must be saline, usually in equal volume. Crystal formation occurs with: more dilute solutions; dextrose solutions; and glass syringes
Half-life	3.5 h after administration into perfusion system	2.3 h in patients with congestive cardiac failure	4–7 h
Effects of impaired renal function	40% of dose excreted unchanged thus dose needs to be reduced	≈80% excreted unchanged thus dose needs reduction, but there are no recommendations as to how much	Mainly hepatic metabolism to enoximone sulphoxide which may accumulate
Contraindications	Hypersensitivity to phosphodiesterase inhibitors or bisulphite	Hypersensitivity to phosphodiesterase inhibitors	Hypersensitivity to phosphodiesterase inhibitors. Hypertrophic cardiomyopathy and untreated stenotic valve disease
Adverse events	Thrombocytopenia, which is dose related and reversible, is observed in about 1 in 40 patients Hypotension is rare	No thrombocytopenia Hypotension observed in about 1 in 30 patients (2.9%)	No thrombocytopenia but very rarely agranulocytosis has been reported Hypotension can be expected if drug infusion is given rapidly
Incompatibilities	Incompatible with frusemide	Incompatible with frusemide and procainamide	None reported

index was seen in those patients whose baseline haemodynamic function was most impaired. This suggests that those who benefit most from this therapy are patients with more impaired, or potentially impaired, cardiac reserve.

Pharmacodynamic studies show a relatively short context-sensitive half-time of PDE III inhibitors after a bolus loading dose, and so it has been recommended that continuous infusion of drug is started promptly after loading.[4] Most studies reported thus far have followed this recommendation. However, more recent experimental data, together with a review of previous study data, question if this approach is universally required.

In particular, Gonzalez and colleagues found no significant correlation between clinical effect of enoximone and serum concentrations of the drug or its active metabolite. Therefore, they suggested that there may be a longer duration of the intracellular actions of the drug than suggested by pharmacokinetic data.[5]

This suggestion is further endorsed by other evidence:

(1) Kikura and colleagues reported no significant difference in haemodynamic improvement between patients treated with a loading bolus alone or a bolus followed by an infusion.[7]

(2) The European milrinone multicentre study[6] found no difference in improvement in cardiac output in patients allocated to a high- or low-dose infusion after a standard loading dose.

(3) When a loading dose of PDE III inhibitor was administered before separation from bypass, there was consistent improvement in haemodynamic state that continued for at least 2 h after operation without the use of a continuous infusion.[10–12] This work has been substantiated by a report from Lobato, Florete and Bingham in this issue of the journal.[14] In these studies, the need for vasoconstrictor therapy to offset any vasodilatation caused by the initial loading with PDE III inhibitor decreased over time, but improvement in cardiac index was sustained.

(4) Badner, Murkin and Shannon[12] also showed that in patients undergoing mitral valve surgery, there was a measurable decrease in systemic vascular resistance in patients treated with amrinone administered before separation from CPB. Nevertheless, there was no associated increase in the amount of vasopressors or inotropes needed to wean from bypass. They demonstrated a significant decrease in mean arterial pressure, only within the first few minutes of administration of amrinone. These patients were on CPB, allowing easy manipulation of either pump flow or use of vasopressor agents at a non-critical time to maintain haemodynamics. As with the European milrinone data,[6] this group also showed a statistically significant inverse relationship between baseline cardiac index and subsequent improvement in haemodynamic variables.

Although the ideal inotrope is currently not available, there are compelling arguments in favour of the use of phosphodiesterase inhibitors with pre-existing ventricular dysfunction, after myocardial revascularization, when postoperative ischaemia is present or when stunning of the myocardium is likely to be present. They appear safe in terms of their arrhythmogenic potential and exert greater effect on those with the worst pretreatment myocardial performance. An extension of this argument could be that if given prophylactically to all patients considered at risk of requiring inotropic therapy in the early postoperative period, they should have little detrimental effect on those patients who subsequently confound expectations and do not need such drugs. An increasing body of evidence suggests that the loading dose alone is crucial and any further infusion of PDE III into the postoperative period, despite decreasing plasma concentrations of drug, may be of little benefit to improve cardiac output. However, prolonged administration may increase the possibility for concurrent vasoconstrictor therapies if vasodilatation becomes prominent.

If the evidence for the use of a loading dose only is confirmed, this suggests that PDE III inhibitors should be increasingly used prophylactically in high-risk patients. For non-cardiac surgery, ease of storage and administration (table 2) suggest that milrinone may be the drug of choice. In cardiac surgical practice, the current evidence shows that this approach offers the opportunity to: avoid a failed wean from bypass thereby reducing the duration of bypass; resolve or prevent ischaemia; and avoid the need for mechanical intervention such as an intra-aortic balloon pump.

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References

1 Lewis PK Early intervention of inotropic support in facilitating weaning from cardiopulmonary bypass: The New England Deaconess Hospital experience. *Journal of Cardiothoracic and Vascular Anesthesia* 1993; 7 (Suppl. 2): 40–45.
2. Butterworth JF, Legault C, Royster RL, Hammon JW. Factors that predict the use of positive inotropic drug support after cardiac valve surgery. *Anesthesia and Analgesia* 1998, **86**: 461–467.
3. Hardy J-F, Belisle S. Inotropic support of the heart that fails to successfully wean from cardiopulmonary bypass: The Montreal Heart Institute Experience. *Journal of Cardiothoracic and Vascular Anesthesia* 1993, 7 (Suppl. 2): 33–39.
4. Butterworth JF, Hines RL, Royster RL, James RL A pharmacokinetic and pharmacodynamic evaluation of milrinone in adults undergoing cardiac surgery. *Anesthesia and Analgesia* 1995; **81**: 783–792.
5. Gonzalez M, Desager J-P, Jaquemart J-L, Chenu P, Muller T, Installe E. Efficacy of enoximone in the management of refractory low-output states following cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 1988; **2**: 409–418.
6. Feneck RO. Intravenous milrinone following cardiac surgery. I. Effects of bolus infusion followed by variable dose maintenance infusion. II. Influence of baseline hemodynamics and patient factors of therapeutic response. *Journal of Cardiothoracic and Vascular Anesthesia* 1992, **6**: 554–567.
7 Kikura M, Levy JH, Michelson LG, Shanewise JS, Bailey JM, Sadel SM, Szlam F. The effect of milrinone on hemodynamics and left ventricular function after emergence from cardiopulmonary bypass. *Anesthesia and Analgesia* 1997; **85**: 16–22
8. Rathmell JP, Prielipp RC, Butterworth JF, Williams E, Villamaria F, Testa L, Viscomi C, Ittleman FP, Baisen CE, Royster RL. A multicenter, randomised, blind comparison of amrinone with milrinone after elective surgery. *Anesthesia and Analgesia* 1998; **86**: 683–690.
9. De Hert SG, Moens MM, Jorens PG, Delrue GL, de Paep RC, Vermeyen KM. Comparison of two different loading

doses of milrinone for weaning from cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia* 1995; **9**: 264–271.

10. Boldt J, Kling D, Zickmann B, Dapper F, Hempelmann G. Efficacy of the phosphodiesterase inhibitor enoximone in complicated cardiac surgery. *Chest* 1990; **98**: 53–58.
11. Boldt J, Knothe C, Zickmann B, Ballesteros M, Russ W, Dapper F, Hempelmann G. The role of enoximone in cardiac surgery. *British Journal of Anaesthesia* 1992; **69**: 45–50.
12. Badner NH, Murkin JM, Shannon NA. An amrinone bolus prior to weaning from cardiopulmonary bypass improves cardiac function in mitral valve surgery patients. *Journal of Cardiothoracic and Vascular Anesthesia* 1994; **8**: 410–414.
13. Butterworth JF, Royster RL, Prielipp RC, Lawless ST, Wallenhaupt SL. Amrinone in cardiac surgical patients with left ventricular dysfunction. *Chest* 1993; **104**: 1660–1667.
14. Lobato EB, Florete O, Bingham HL. A single dose of milrinone facilitates separation from cardiopulmonary bypass in patients with pre-existing left ventricular dysfunction. *British Journal of Anaesthesia* 1998; **81**: 782–784.

British Journal of Anaesthesia 1998; **81**: 667–668

EDITORIAL II

Gastrointestinal tonometry comes of age?

Monitoring of gut mucosal perfusion is of established clinical interest.[1–3] There are many methods available to aid the clinician in the diagnosis and monitoring of gut mucosal ischaemia but few are of practical use in the clinical domain. The only clinical monitor currently available that can provide such information and is practical for use during routine practice is the gastrointestinal tonometer.[2–4]

Tonometry refers to measurement of partial pressure of a gas. Gastrointestinal tonometry uses a modified nasogastric tube to allow measurement of carbon dioxide tension in the lumen of the gastrointestinal tract. This measurement, when used in combination with arterial bicarbonate, can be used to estimate the intramucosal pH (pHi) of the gastrointestinal tract. Despite several fundamental flaws in the tonometric technique, experimental studies have shown that mucosal acidosis (measured with the gastrointestinal tonometer) correlates with reduced mucosal perfusion and/or the onset of anaerobic metabolism in response to hypovolaemia, hypoxaemia and sepsis.[3,4]

The clinical use of gastrointestinal tonometry remains controversial, despite an impressive clinical research record. In many, although not all, published studies of patients admitted to adult intensive care units, an abnormally low pHi value has been found to be common and associated with a poor outcome. In a prospective, randomized, multicentre study of pHi-guided therapy, a >25% improvement in survival was reported in patients admitted to the ICU with a normal pHi.[5] Numerous published studies on hundreds of patients have examined the relationship between pHi and outcome after accidental trauma or major surgery and have concluded that the presence of a low pHi is a predictor of poor outcome.[6] In studies that compared tonometry with other routinely used monitors of cardiorespiratory function, it has been found to be a more sensitive predictor of morbidity than global measures such as arterial pressure, cardiac output or urine flow measurement.[6] In a prospective, randomized study of trauma patients, Ivatury and colleagues compared PA catheter oxygen delivery–oxygen consumption-guided therapy with pHi-guided therapy.[7] They found that patients who corrected their pHi by 24 h had a better outcome, irrespective of the treatment group, and there was a marked trend towards improved outcome in the pHi-guided group. We have reported the results of a prospective, randomized study of the effects of fluid loading patients undergoing elective cardiac surgery with the aim of maintaining perioperative gastric mucosal perfusion.[8] We found that the incidence of a low pHi was significantly reduced in the study group compared with controls, as were the number of major complications and days spent in hospital. Marik, Iglesias and Maini reported similar findings in patients undergoing aortic surgery with regards to pHi but not outcome.[9] In both studies, pHi was used as an outcome variable but not as a monitor to guide therapy.

A monitor is a warning device that detects a physiological abnormality allowing the physician to intervene to correct the abnormality with the hope that it is associated with an improvement in outcome. Aside from the concerns surrounding the whole concept of gastrointestinal tonometry and whether or not it can be used as a measure of tissue perfusion–oxygenation, there are major concerns about the practicalities of the established saline catheter technique. First, the numerous steps involved mean that it is prone to many systematic errors. Second, as highlighted by Kolkman and colleagues in this isssue of the journal, equilibration of carbon dioxide with saline within the tonometer balloon is never complete and thus a time-dependent correction factor is required.[10] Third, routinely used blood-gas analysers are not well designed for measurement of carbon dioxide in saline, and bias and imprecision are common.[11] Fourth, the fact that it is a manual system with a long equilibration period makes it virtually impossible to use as a true monitor in the setting of acute resuscitation (e.g. during major surgery).

The introduction of the Tonocap (Instrumentarium Corp., Helsinki, Finland) is an important advance. The Tonocap is designed to use the same TRIP tonometer catheters (Instrumentarium Corp., Helsinki, Finland) that were used for saline tonometry. The device inflates the balloon on the end of the catheter with a small volume of air, allows for equilibration with the gastrointestinal environment, then automatically aspirates the balloon content. The gas from the balloon is analysed using the same infra-red method used to measure expired gas mixtures. The sample is then replaced into the balloon to decrease the equilibration time for the next.

We have seen reports previously of *in vitro* testing, suggesting many of the systematic errors involved in balloon saline tonometry and concerns about equilibration times have been eliminated.[12–15] The Tonocap has minimal bias and excellent precision for determination of $P\text{CO}_2$ *in vitro*. As with any monitoring device, *in vivo* use is associated with a reduction in precision.[15–17] One of the difficulties in determining performance in patients is the lack of a gold standard for measurement of tissue $P\text{CO}_2$. Therefore, when saline tonometry is used as a gold standard we should not be surprised to see a large scatter, as reported in the study of Janssens and colleagues[16] in this issue of the journal. *In vitro* testing has shown that the saline method has a fixed negative bias and a much higher degree of imprecision.[15–17]

The fact that the Tonocap combines both end-tidal and gastrointestinal luminal carbon dioxide measurement could mean that arterial blood-gas analysis will no longer be an essential component of gastrointestinal tonometry. The calculated pHi concept is already unpopular as it is influenced markedly by acid–base disturbances that may be independent of gut perfusion. Gastrointestinal $P\text{CO}_2$ is uninterpretable without reference to arterial carbon dioxide, as both are directly influenced by alveolar ventilation.

This has led to the popularization of the "CO_2 gap" (i.e. gastrointestinal $P\mathrm{co}_2$–arterial $P\mathrm{co}_2$). However, calculation of the CO_2 gap demands arterial blood-gas analysis and thus reduces the value of automated online tonometry measurements: it is unlikely that blood-gas analysis is performed every 10 min. The automated calculation of the gastrointestinal–end-tidal $P\mathrm{co}_2$ gap could overcome all of these issues. At first glance, an obvious source of error lies in the well recognized gradient between end-tidal and arterial carbon dioxide and the influence of ventilation–perfusion mismatching on physiological deadspace. On more careful consideration, these may not be real problems in clinical practice. First, all monitors are most useful as trend indicators providing there is confidence in the quality of signal—we already accept this limitation with routine use of end-tidal $P\mathrm{co}_2$ measurement. Second, any increase in physiological deadspace secondary to reduced pulmonary perfusion tends to exaggerate the gap between end-tidal and gastrointestinal $P\mathrm{co}_2$ rather than reduce it. This may expose some patients to unnecessary treatment but will not leave patients with dangerously covert gut mucosal hypoperfusion.

There are several issues that need careful consideration before we accept the Tonocap as a direct substitute for saline tonometry: (i) the Tonocap has eliminated negative bias associated with the saline measurement, thus direct comparisons with saline data are of limited value; (ii) the Tonocap and in particular gastrointestinal–end-tidal $P\mathrm{co}_2$ needs independent investigation and validation; (iii) the vast majority of the previously published tonometry data were collected using the saline method and calculation of pHi. A leap of faith to "CO_2 gap" means the metabolic component from arterial bicarbonate is lost and therefore one should not necessarily assume that the predictive ability will be as high;[4] and (iv) it is inevitable that any new monitor is associated with a list of artefacts not anticipated by the manufacturers and these will only come to light with clinical experience.

In summary, with the clinical availability of the Tonocap, gastrointestinal tonometry has come of age. If we choose to measure the $P\mathrm{co}_2$ of a patient's gastrointestinal tract, it can be done more easily and reliably than ever before using the Tonocap. Should we bother? Well, who knows? It is a decision we have to make for ourselves. Awaiting the results of large, prospective, randomized, multicentre studies is unlikely to provide answers that will enhance our decision. There is no precedent for a physiological monitor used in anaesthetics. Traditionally, we have said if we can detect and correct a physiological abnormality (e.g. hypoxaemia and the pulse oximeter) then that is good enough. A monitor is not a therapy and as such cannot influence outcome. A monitor can only guide therapeutic intervention. Therefore, it is extremely unlikely that anyone will ever organize or fund a study that will support or refute the suggestion that the Tonocap will help you to help your patients. Sad, but true.

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References

1. Dantzker DR. Monitoring tissue oxygenation—The search for the grail. *Chest* 1997; **111**: 12–14.
2. Rombeau JL, Takala J. Gut dysfunction in critical illness *Clinical Nutrition* 1997; **16**: 57–60.
3. Gutierrez G, Brown SD. Gastrointestinal tonometry· a monitor of regional dysoxia. *New Horizons* 1996; 4: 413–419.
4. Mythen MG, Faehnrich J. Monitoring gut perfusion. In: Rombeau JL, Takala J, eds. *Gut Dysfunction in Critical Illness*. Berlin: Springer Verlag, 1997; 246–263.
5. Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi A, Jorge M, Pusajo J, Klein F, San Roman E, Dorfman B, Schottlender J, Giniger R. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; **339**: 195–199.
6. Mythen MG, Hamilton-Davies C, Webb AR. Peri-operative gastrointestinal tonometry. In: Vincent JL, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin: Springer, 1996; 227–240.
7. Ivatury RR, Simon RJ, Havriliak D, Garcia G, Greenbarg J, Stahl WM. Gastric mucosal pH and oxygen delivery and oxygen consumption indices in the assessment of adequacy of resuscitation after trauma: a prospective, randomised study. *Journal of Trauma* 1995; **39**: 128–136.
8. Mythen MG, Webb AR. Per-operative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Archives of Surgery* 1995; **130**: 423–429.
9. Marik PE, Iglesias J, Maini B. Gastric intramucosal pH changes after volume replacement with hydroxyethyl starch or crystalloid in patients undergoing elective abdominal aneurysm repair. *Journal of Critical Care* 1997; **12**: 51–55.
10. Kolkman JJ, Steverink PJGM, Groeneveld ABJ, Meuwissen SGM Characteristics of time-dependent $P\mathrm{co}_2$ tonometry in the normal human stomach. *British Journal of Anaesthesia* 1998; **81**: 669–675.
11. Knichwitz G, Mertes N, Kuhmann M. Improved pCO_2 measurement in six standard blood gas analysers using a phosphate buffered solution for gastric tonometry. *Anaesthesia* 1995; **50**: 532–534.
12. Kolkman JJ, Zwaarekant LJ, Boshuizen K, Groeneveld ABJ, Meuwissen SGM. In vitro evaluation of intragastric PCO_2 measurement by air tonometry. *Journal of Clinical Monitoring* 1997; **13**: 115–119.
13. Noone R, Mythen MG, Vaslef S. In-vitro validation of an automated on-line gastrointestinal tonometer (The Tonocap). *Critical Care Medicine* 1997; **25**: A137.
14. Noone RB, Mythen MG, Vaslef SN. A comparison of the response of the Tonocap and saline tonometry to a change in CO_2. *Critical Care* 1997; **1**: P88.
15. Creuter J, De Backer D, Vincent JL. Monitoring gastric mucosal carbon dioxide pressure using gas tonometry: In vitro and in vivo validation studies. *Anesthesiology* 1997; **87**: 504–510
16. Janssens U, Graf J, Koch KC, Hanrath P. Gastric tonometry: *in vivo* comparison of saline and air tonometry in patients with cardiogenic shock. *British Journal of Anaesthesia* 1998; **81**: 676–680.
17. Noone R, Urakubo A, Mythen MG, Vaslef S. Comparison of gastrointestinal tonometry using the saline technique with an automated air device (The Tonocap®) in swine. *Critical Care Medicine* 1997; **25**: A137.

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CLINICAL INVESTIGATIONS

Characteristics of time-dependent $P\mathrm{CO}_2$ tonometry in the normal human stomach

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Summary

Factors that affect $P\mathrm{CO}_2$ measurement in balloon saline during gastrointestinal tonometry are unclear. They include carbon dioxide diffusion rate, correction factors for calculation of equilibrium $P\mathrm{CO}_2$ from measurements at saline dwell times that are shorter than needed for full equilibration, role of blood-gas analyser bias during *ex vivo* $P\mathrm{CO}_2$ measurements in saline, and normal values for intragastric $P\mathrm{CO}_2$ (Pi_{CO_2}) and intramucosal pH (pHi) at equilibrium, and their differences from blood values. In a laboratory study, normal $P\mathrm{CO}_2$ changes in a saline-filled tonometer balloon placed in a saline bath at constant $P\mathrm{CO}_2$ were described by a non-linear model, with a half-time of mean 4.4 min and 95% equilibration at mean 83 min. In a study in 20 healthy volunteers, Pi_{CO_2} build up in a saline-filled tonometer balloon placed in the stomach, measured at dwell times of 10, 20, 30 and 60 min, was slightly ($P < 0.05$) slower than *in vitro*, with a half-time of mean 5.8 min and 95% equilibration at mean 110 min. Correction factors to derive equilibrium Pi_{CO_2} at short dwell times and independently from blood-gas analyser bias were calculated. The factors differed ($P<0.05$) from those currently provided by the manufacturer. Normal threshold values (mean) were: equilibrium $Pi_{\mathrm{CO}_2} \leq 6.6$ kPa, pHi ≥ 7.33, Pi_{CO_2} to blood $P\mathrm{CO}_2$ difference ≤ 1.1 kPa and pH difference ≥ -0.06. Pi_{CO_2} did not differ from, and was directly related to, blood $P\mathrm{CO}_2$. These values provide a reference base for other studies and show that gastric mucosal $P\mathrm{CO}_2$ depends on alveolar ventilation if blood flow is adequate. (*Br J. Anaesth.* 1998; **81**: 669–675)

Keywords: carbon dioxide, measurement; gastrointestinal tract, pH; measurement techniques, tonometry

An increased intragastric $P\mathrm{CO}_2$ (Pi_{CO_2}), as measured by tonometry, or its derivative, decreased intramucosal pH (pH_i), suggests inadequate gastric mucosal blood flow.[1–4] If blood flow is sufficient and acid secretion is suppressed to avoid generation of carbon dioxide from bicarbonate buffering of gastric acid, Pi_{CO_2} approximates supplying blood $P\mathrm{CO}_2$.[5–7] Increased Pi_{CO_2} relative to blood $P\mathrm{CO}_2$ during ischaemia stems from a reduced washout of metabolically produced carbon dioxide after hypoperfusion and from buffering of anaerobically produced lactic acid by bicarbonate.[8] Even though intramucosal bicarbonate may not be the same as the supplying blood bicarbonate content,[9] pHi, calculated from Pi_{CO_2} and blood bicarbonate content using the Henderson–Hasselbalch equation, is often used as a measure of the adequacy of gastric mucosal blood flow. Clinical studies in critically ill patients suggest that a low pHi is predictive of a poor prognosis[10–14] and that pHi can guide therapy and improve survival.[15 16] Although tonometry is a promising tool for assessment of adequacy of regional blood flow in critically ill patients, it has not gained wide acceptance, partly because of methodological uncertainties.

Pi_{CO_2} is measured *ex vivo* in saline aspirated from the intragastric tonometer balloon, after a given dwell time. To calculate the equilibrium Pi_{CO_2} from dwell times shorter than the time needed for full equilibration, which exceeds 60 min, measured Pi_{CO_2} is multiplied by dwell time-dependent correction factors. These factors are provided by the manufacturer of the tonometer.[17 18] However, the normal rate of Pi_{CO_2} change in the tonometer balloon *in vitro* and in the normal human stomach, and thereby the validity of the correction factors, taking into account the recently described catheter deadspace effect and $P\mathrm{CO}_2$ measurement bias in saline by most blood-gas analysers,[19–24] are virtually unknown. Consequently, the normal ranges of equilibrium Pi_{CO_2} and pHi and their differences from blood values are unclear. The lower limit of normal pHi, for example, may vary between 7.31 and 7.35.[7 10 11 13 15 25–27] Finally, the premise that long dwell times yield more accurate Pi_{CO_2} assessments than shorter ones is unproved.[24]

In this study, we assessed normal Pi_{CO_2} build-up in the tonometer balloon *in vitro* and in the stomach of healthy volunteers. We intended to provide a reference base for manual saline tonometry and thereby widen its clinical use, particularly if semicontinuous automated air tonometry (a technique that circumvents some of the methodological problems associated with saline tonometry) is not yet available.[23 28–30]

Subjects and methods

The *in vitro* study was performed at the Department of General and Large Animal Surgery, University of

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Utrecht. The volunteer study was performed at the Free University Hospital, Amsterdam. The study was approved by the Local Ethics Committee.

For the *in vitro* study, a steady state $P\text{CO}_2$ in a 5-litre, temperature-controlled (mean 37.0 (SD 0.2)°C) 0.9% saline-filled glass tank was achieved by bubbling carbon dioxide calibration gases (4.98% and 9.98% in nitrogen, accuracy 1%; NTG, Tilburg, The Netherlands) at a flow rate of 5 litre min^{-1} via a microporous device placed on the bottom of the tank. There was a small hole in the rubber cover of the tank for gas insufflation and one for gas venting. Bath $P\text{CO}_2$ was assumed to have reached steady-state after approximately 3 h when five consecutive determinations at 5-min intervals differed by less than 5%. Bias (mean difference from expected $P\text{CO}_2$) and precision (SD of the bias) of $P\text{CO}_2$ measured in saline with the blood-gas analyser (ABL 505, Radiometer, Copenhagen, Denmark) was determined by comparison of the measured bath $P\text{CO}_2$ at steady state with the expected bath $P\text{CO}_2$. The latter was calculated from the carbon dioxide content of the calibration gas, bath temperature and barometric pressure (*P*bar), according to the gas law expressed in the equation $P\text{CO}_2=(P\text{bar}-47)\times 100\times\%\text{CO}_2$ content, where 47 mm Hg represents water vapour pressure. With the blood-gas analyser used in this experiment, bias was –6.8% and precision 3.0%, in agreement with the literature.[21] Thus for the *in vitro* experiment, all $P\text{CO}_2$ measurements in saline were multiplied by a factor of 1.07 (=100/93.2). Using this factor, measured bath $P\text{CO}_2$ was mean 4.8 (SD 0.2) kPa and 9.4 (0.2) kPa, at an expected bath $P\text{CO}_2$ of 4.8 kPa and 9.5 kPa, respectively. $P\text{CO}_2$ at the start and end of the experiment was 4.8 (0.2) kPa and 34.7 (0.2) kPa, respectively, at low bath $P\text{CO}_2$, and 9.4 (0.2) kPa and 9.4 (0.1) kPa, respectively, at high bath $P\text{CO}_2$, indicating steady state during the experiment.

$P\text{CO}_2$ increase was determined in six sigmoid-type tonometers (TRIP, Tonometrics, Bethesda, ML, USA), consisting of a silastic nasogastric tube impermeable to carbon dioxide with a volume of approximately 1.0 ml, and a silicone carbon dioxide permeable balloon with a volume of 2.5 ml. These were placed in the saline bath at steady state $P\text{CO}_2$, after balloon saline dwell times of 10, 20, 30, 45, 60, 90 and 120 min. Measurements were performed for each tonometer at both expected bath $P\text{CO}_2$ concentrations of 4.8 and 9.5 kPa. For each dwell time, saline 2.5 ml was introduced into the tonometer balloon. After a given dwell time, saline was aspirated and the first 1.0 ml was considered to represent deadspace. Between dwell times, the tonometer was rinsed four times with 2.5 ml of fresh saline to remove all saline in the deadspace compartment, to avoid contamination of reintroduced saline by the fluid remaining in the deadspace after prior aspiration.[24]

For the *in vivo* study, we studied 20 healthy volunteers, aged 21–26 (mean 23) yr, after obtaining informed consent. Volunteers did not eat or smoke for 10 h before the study, and did not drink for 2 h before or during the study. Volunteers were seated during the study. A glass electrode for continuous gastric juice pH measurement with integral Ag/AgCl reference electrode near its tip (Ingold 440, Ingold Messtechnik, Urdorf, Switzerland) was introduced via the nose into the stomach. Using direct pH measurement, the electrode was placed 10 cm beyond the gastro-oesophageal junction, which was recognized by an abrupt pH decrease. The pH electrode was connected to a recorder which stored mean pH every 8 s using a hospital-developed microcomputer system for pH analysis.[31] A tonometer (TRIP, Tonometries Inc., Bethesda, ML, USA), sigmoid type, was repeatedly filled and emptied using saline to remove all air. We used the sigmoid-type catheter as it is better tolerated by healthy volunteers than the gastric type.[5] The tonometer was placed via the nose, the same distance as the pH electrode. In each subject, 2 h after tonometry was started, gastric acid secretion was suppressed by an i.v. bolus dose of ranitidine 100 mg, followed by continuous infusion of 25 mg h^{-1} via an infusion pump (Limed P55-330, Limed, Amsterdam, The Netherlands). Gastric acid secretion was suppressed to prevent buffering of gastric acid by bicarbonate, thereby increasing Pi_{CO_2} independently from mucosal $P\text{CO}_2$.[5 6 30] We aimed to have a constant gastric juice pH>4.0. In fact, 2 h after the start of drug infusion and before tonometry, gastric juice pH was 5.6 (1.5) and >4.0 in each volunteer. pH remained >4.0 for 92(3)% of the study time, indicating sufficient inhibition of gastric acid secretion for tonometry.[5] We used saline for gastric tonometry as saline is commonly used and allows for relatively rapid balloon Pi_{CO_2} build-up and for accurate measurements provided that an adequately anaerobic technique is used and blood-gas analyser bias is known.[19 22] In each volunteer, Pi_{CO_2} was measured after sequential saline dwell times in the tonometer balloon of 10, 20, 30 and 60 min. At the start of each measurement, 2.5 ml of fresh saline was introduced into the tonometer balloon. After a given dwell time, saline was aspirated and the first 1.0 ml, containing the deadspace volume of the catheter, was discarded. The next 1.5 ml was aspirated into a 2.5-ml polypropylene syringe (Monoject, Sherwood Medical, Ballymoney, Northern Ireland) which was closed with a plastic cap (Capillary caps, Ciba-Corning, Sudbury, UK). In this sample, Pi_{CO_2} was measured within 15 min, using a blood-gas analyser (Corning 278, Ciba-Corning, Houten, The Netherlands). Bias and precision for $P\text{CO}_2$ measurements in saline with this blood-gas analyser were determined, as described above. Bias was –15% and precision 3%, in agreement with the literature.[19 22] Thus all measured Pi_{CO_2} values in saline in the volunteer study were multiplied by 1.18 (=100/85). When we did this volunteer study we were unaware of the catheter deadspace effect as a source of measurement error at short dwell times.[24] Fresh saline was introduced for the 10-min dwell times. Overestimation of Pi_{CO_2} in the next measurement with the 20-min dwell time caused by the deadspace effect amounts to 6%.[24] Hence, the 20-min Pi_{CO_2} data were corrected accordingly. The index finger of each subject was warmed in water for 3 min and two arterialized blood samples were obtained, one at the start and one at the end of the study. From these capillary samples, pH (cpH), bicarbonate content (cBic, mmol litre^{-1}) and $P\text{CO}_2$ (Pc_{CO_2}, kPa) were determined using a Corning 278 blood-gas analyser. Values in carefully drawn capillary blood approximate those in arterial blood.[32]

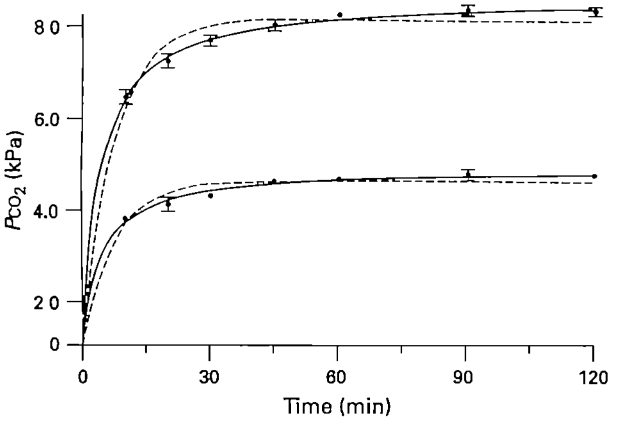

Figure 1 $P\mathrm{co}_2$ increase (mean SD) for six tonometers placed in saline baths at a steady state $P\mathrm{co}_2$ of mean 4.8 and 9.4 kPa The curves were derived from model 2 (see text; solid line) and model 1 (broken line), for mean values. The latter model fitted the data less well than the former, since calculated $P\mathrm{co}_2$ at equilibrium was 5% lower than bath values.

CALCULATIONS AND STATISTICAL ANALYSIS

For the *in vitro* experiments, the kinetics and equilibrium of $P\mathrm{co}_2$ build-up were assessed by the least squares technique and non-linear regression analysis according to models 1 and 2. For model 1: $P\mathrm{co}_2(t)=P\mathrm{co}_2$ at equilibrium$\times(1-e^{-kt})$; for model 2: $P\mathrm{co}_2(t)=P\mathrm{co}_2$ at equilibrium$\times t/(T_{\frac{1}{2}}+t)$. $P\mathrm{co}_2(t)$ is $P\mathrm{co}_2$ measured after t min, k is a constant, $T_{\frac{1}{2}}$ is the half-time of $P\mathrm{co}_2$ increase and t is time in minutes. The goodness of fit of the models was evaluated by the coefficient of determination (r^2) and the ability of estimated equilibrium $P\mathrm{co}_2$ to predict bath $P\mathrm{co}_2$. For the *in vivo* study, a curve according to model 2 that best represented the *in vitro* data, was used to describe the course of measured Pi_{CO_2} values. Time-dependent correction factors were calculated according to: correction factor $(t)=Pi_{\mathrm{CO}_2}$ at equilibrium $Pi_{\mathrm{CO}_2}(t)$. The means of the dwell time-dependent correction factors were used to estimate the equilibrium Pi_{CO_2} from $Pi_{\mathrm{CO}_2}(t)$ at each dwell time. The coefficient of variation (CV=SD/mean) was used as an index of reproducibility of equilibrium Pi_{CO_2} assessments at each dwell time. pHi was calculated according to the (Henderson–Hasselbalch equation from pHi=6.1+log (cBic/(0.03$\times Pi_{\mathrm{CO}_2}$ at equilibrium)). Linear regression analysis was used to correlate equilibrium Pi_{CO_2} with Pc_{CO_2}. We calculated normal values for the tonomeric variables at each dwell time, using individually measured values multiplied by the mean dwell time-dependent *in vivo* correction factor, and for the values estimated at equilibrium in each patient. The threshold values were defined as mean (±2 SD) where appropriate. Data are expressed as mean (SD) or range, where appropriate. $P<0.05$ was considered statistically significant.

Results

IN VITRO STUDY

$P\mathrm{co}_2$ increase in the tonometers at each bath $P\mathrm{co}_2$, calculated according to models 1 and 2, is shown in figure 1. Both types of curves fitted well: mean r^2 was 0.96 for model 1 and 0.98 for model 2. However, $P\mathrm{co}_2$ at equilibrium calculated with model 1 was lower than measured bath $P\mathrm{co}_2$: 8.8 (0.2) kPa *vs* 9.4 (0.2) kPa ($P<0.001$) and 4.5 (0.1) kPa *vs* 4.8 (0.2) kPa ($P<0.001$) for high and low bath $P\mathrm{co}_2$, respectively.

Table 1 Correction factors for calculation of equilibrium Pi_{CO_2} from measured Pi_{CO_2} corrected for blood-gas analyser bias (mean (SD)). †††$P<0.001$ *vs* manufacturer's correction factor, *$P<0.05$ *vs in vitro*

Dwell time (min)	Manufacturer	Our study *In vitro*	Our study *In vivo*
10	1.57	1.44 (0.05)†††	1.58 (0.17)*
20	1.39	1.22 (0.02)†††	1 29 (0 09)†††
30	1.29	1.15 (0.02)†††	1.19 (0.06)†††
45	1.19	1.10 (0.01)†††	1.13 (0.04)†††
60	1.17	1.07 (0.01)†††	1.10 (0 03)†††
120	1.17	1.04 (0.01)†††	1.05 (0.02)†††

$P\mathrm{co}_2$ at equilibrium, calculated using model 2, did not differ from measured bath values: 9.5 (0.1) *vs* 9.4 (0.2) and 4.8 (0.1) *vs* 4.8 (0.2) kPa. Therefore, model 2 was used for the subsequent evaluation of $P\mathrm{co}_2$ build-up in volunteers. According to model 2, *in vitro* $T_{\frac{1}{2}}$ was 4.4 (0.5) min and mean time to reach 95% equilibration was 83 min. The dwell time-dependent correction factors *in vitro* are given in table 1. They differed from those provided by the manufacturer.

Estimated $P\mathrm{co}_2$ at equilibrium, using mean correction factors for multiplication with measured $P\mathrm{co}_2$ were, at an expected bath $P\mathrm{co}_2$ of 4.8 kPa, 5.0 (0.1) kPa (CV 1.8%) at the 10-min dwell time, 4.7 (0.2) kPa (CV 3.5%) at the 20-min dwell time, 4.7 (0.1) kPa (CV 2.0%) at the 30-min and 4.9 (0.1) kPa (CV 1.5%) at the 60-min dwell time. At an expected bath $P\mathrm{co}_2$ of 9.5 kPa, estimated $P\mathrm{co}_2$ at equilibrium was at the 10-min dwell time 9.7 (0.2) kPa (CV 1.6%), at the 20-min dwell time 9.4 (0.2) kPa (CV 2.3%), at the 30-min dwell time 9.5 (0.2) kPa (CV 2.0%) and at the 60-min dwell time 9.7 (0.2) kPa (CV 1.5%). Hence, estimation of expected $P\mathrm{co}_2$ was accurate, independent of dwell time.

IN VIVO STUDY

Pi_{CO_2} build-up in vivo

The rate of Pi_{CO_2} increase *in vivo* was slower than *in vitro* ($T_{\frac{1}{2}}$ of 5.8 (1.9) min, $P<0.05$ *vs in vitro*) (Fig. 2). Mean r^2 was 0.95. Calculated Pi_{CO_2} at equilibrium was 5.7 (0.5) kPa, while 95% equilibration was reached at mean 110 min ($P<0.05$ *vs in vitro*). The *in vivo* correction factors differed from those supplied by the manufacturer. The *in vivo* and *in vitro* correction factors differed at the 10-min dwell time only (table 1). Note that the *in vivo* correction factors were independent of blood-gas analyser bias. The CV values of the Pi_{CO_2} measurements were 12%, 11%, 9% and 10%, at 10-, 20-, 30- and 60-min dwell times, respectively (table 2), which were higher than those *in vitro* but independent of dwell time, so that short dwell times should allow for accurate estimation of equilibrium Pi_{CO_2}. Table 2 also shows pHi and differences between tonometric and blood variables at each dwell time.

Capillary blood

For capillary blood samples, there were no differences between initial and final values. Mean cpH was

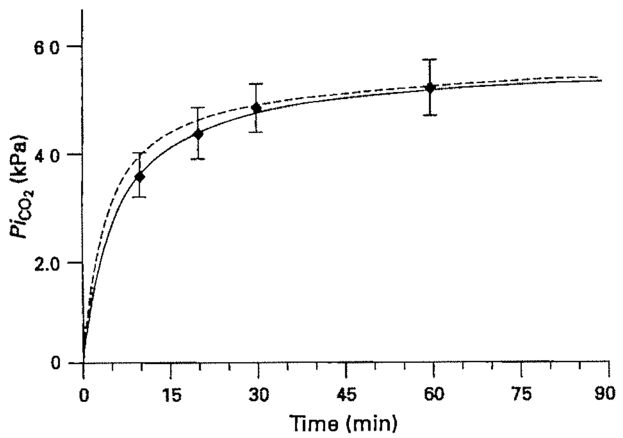

Figure 2 Pi_{CO_2} increase (mean, SD) in tonometers placed in the stomach in 20 healthy volunteers. The curve was calculated for mean values, according to model 2 (solid line) and that based on *in vitro* experiments according to model 2 (broken line).

7.39 (0.01), Pc_{CO_2} 5.5 (0.4) kPa and cBic 24.8 (0.9) mmol litre^{-1}. Pc_{CO_2} and cpH did not differ from Pi_{CO_2} and pHi, respectively.

Normal tonometry values

Table 3 shows normal values for the tonometric variables and their differences from blood values. There was a significant correlation between equilibrium Pi_{CO_2} and Pc_{CO_2} (fig. 3), suggesting that Pi_{CO_2} is partly determined by blood PCO_2 supplying the gastric mucosa.

Error analysis: correction for incomplete equilibration and for blood-gas analyser bias

Using the dwell time-dependent correction factors provided by the manufacturer without correcting for blood-gas analyser bias, the expected Pi_{CO_2} calculated with the correction for blood-gas analyser bias and with the *in vivo* correction factors of this study was underestimated, particularly at short dwell times (table 4). If the correction for blood-gas analyser bias is superimposed on the manufacturer's dwell time-dependent correction factors, Pi_{CO_2} is overestimated, particularly at long dwell times (table 4). The lower limit of normal pHi would thus vary, whether or not correction for blood-gas analyser bias is superimposed on the manufacturer's correction factors for calculation of equilibrium Pi_{CO_2} and whether short or long dwell times are used, between 7.38 (at 16% underestimation of expected Pi_{CO_2} of 6.6 kPa) and 7.26 (at 12% overestimation of Pi_{CO_2} of 6.6 kPa), respectively, compared with 7.31 at an expected Pi_{CO_2} of 6.6 kPa.

Discussion

In this study, we have provided normal values for variables derived from gastric tonometry. From Pi_{CO_2} increase in the *in vitro* experiments and in the human stomach, new correction factors, different from those supplied by the manufacturer, were calculated to allow for saline dwell times shorter than needed for full equilibration. With the use of validated correction factors and the known blood-gas analyser-dependent PCO_2 measurement bias,[19 20 22] Pi_{CO_2} can be assessed accurately.

Table 3 Normal *in vivo* threshold values

	Dwell time (min)				Equilibrium
	10	20	30	60	
Pi_{CO_2} (kPa)	≤6.9	≤6.9	≤6.7	≤6.8	≤6.7
Pi_{CO_2}–blood PCO_2 (kPa)	≤1.1	≤1.3	≤1.3	≤1.2	≤1.1
pHi	≥7.31	≥7.30	≥7.31	≥7.31	≥7.33
pHi–blood pH	≥-0.09	≥-0.08	≥-0.09	≥-0.06	≥-0.06

Our results showed that Pi_{CO_2} build-up in the tonometer in the human stomach was slower than *in vitro*. Coverage of the tonometer balloon by mucus in the stomach may reduce the diffusion rate. The clinical effect of a slower Pi_{CO_2} build-up is small and limited to short dwell times. The use of *in vitro* correction factors would lead to 10% and 5% underestimations of the expected Pi_{CO_2} at 10- and 20-min dwell times, respectively, so that, in contrast with common practice, the use of *in vitro* correction factors for *in vivo* measurements seems inappropriate. For a dwell time of 30 min in clinical studies, the *in vitro* correction factor can be used, as it does not differ from that *in vivo*. The *in vitro* correction factors found previously largely corresponded to ours, although it is unclear how they were derived.[23] The larger CV values of Pi_{CO_2} in *in vivo* than in the *in vitro* study may be explained by varying Pi_{CO_2} between individuals rather than a higher measurement error *in vivo*. In other respects, the variability of *in vivo* Pi_{CO_2} assessments was independent of dwell-time, and therefore reliable Pi_{CO_2} assessments at short dwell times are practicable.[24]

As our correction factors are independent of blood-gas analyser bias, the use of our factors by others during PCO_2 tonometry should be supplemented by correction for PCO_2 measurement specific for the type of blood-gas machine and the tonometer fluid used.[19–22] The higher correction factors supplied by the manufacturer than our *in vitro* factors may thus have included, contrary to common belief,[7] blood-gas analyser bias for measurements in saline. We learned that the *in vitro* experiments performed by the manufacturer to develop correction factors involved numerous simultaneous measurements of tonometric balloon and surrounding bath PCO_2 at various dwell times in a randomized order, while blood-gas analyser bias for PCO_2 measurements in saline had not been appreciated (J. Kent,

Table 2 Equilibrium Pi_{CO_2}, pHi and differences with blood PCO_2 and pH assessed at various dwell times *in vivo*

Dwell time (min)	Pi_{CO_2} (kPa)	Pi_{CO_2}–blood PCO_2 (kPa)	pHi	pHi–blood
10	5.6 (0.6) [4.5/6.9]	0.1 (0.4) [–0.8/1.0]	7.39 (0.04) [7.33/7.47]	0.00 (0.04) [–0.06/+0.07]
20	5.7 (0.5) [4.9/7.0]	0.3 (0.6) [–0.7/1.4]	7.38 (0.04) [7.30/7.46]	–0.01 (0.04) [–0.08/+0.06]
30	5.7 (0.5) [4.9/6.7]	0.2 (0.5) [–1.0/1.2]	7.38 (0.04) [7.32/7.48]	–0.01 (0.04) [–0.06/+0.08]
60	5.7 (0.5) [4.8/6.7]	0.2 (0.4) [–0.4/1.1]	7.39 (0.04) [7.32/7.44]	0.00 (0.03) [–0.06/+0.05]
Equilibrium	5.7 (0.5) [4.8/6.5]	0.2 (0.4) [–0.4/1.0]	7.39 (0.03) [7.34/7.44]	0.00 (0.03) [–0.05/+0.05]

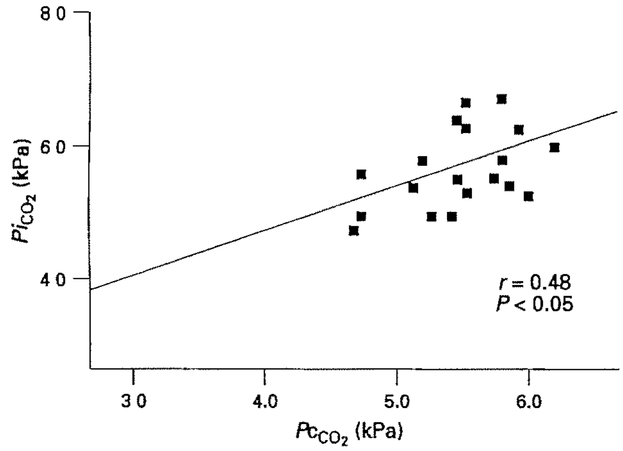

Figure 3 Equilibrium Pi_{CO_2} *vs* Pc_{CO_2}. Solid line=regression line.

Tonometrics, personal communication). The idea that the factor of blood-gas analyser bias has been erroneously incorporated into the manufacturer's correction factors is supported by a correction factor at 120 min of 1.17 for the sigmoid and 1.11 for the gastric tonometer, at a time when equilibration approaches 96% and should be associated with a correction factor of only 1.04.

If a correction for blood-gas analyser bias is superimposed on the manufacturer's correction factors for measurements in saline, overestimation of Pi_{CO_2} and underestimation of pHi results, particularly at long dwell times. This may explain a normal mean pHi of as low as 7.31, found in healthy volunteers by others, using both correction for blood-gas analyser bias and the manufacturer's dwell time-dependent correction factors.[7] Nevertheless, our normal variables largely agree with those found in healthy volunteers in a recent study,[30] even though the latter study does not provide information on correction factors and measurement bias. Finally, a slightly negative tonometer balloon–blood Pco_2 difference was found in a few subjects in our study, contrary to expectations based on normal physiology.[6] A negative difference could be explained by a fall within the tonometer and blood Pco_2 measurement error, that would be approximately 5% at maximum, if both the blood and tonomeric assessments, as judged from the CV values of the tonometer Pco_2 measurements *in vitro*, carry an error of approximately 2.5%.

The catheter deadspace, serving as a reservoir for the Pi_{CO_2} increase,[24] may help to explain why model 2 fitted the measured data better than model 1. The deadspace reservoir effect depends on the volume and diffusion capacity of the balloon and the volume of the tonometer catheter lumen, so that the correction factors would become dependent on the catheter type used.[24] For example, we have shown that a 50% increase in length increased the $T_{\frac{1}{2}}$ of the balloon Pi_{CO_2} increase by 20% and resulted in higher correction factors at 10- and 20-min dwell times.[24] As the gastric tonometer commonly used in critically ill patients is approximately 30% shorter than the sigmoid type, Pi_{CO_2} increase will be 10% faster.[24] From the data in our previous study,[24] it can be estimated that the correction factor at the 10-min dwell time would be approximately 4% less for the gastric than for the sigmoid tonometers used *in vivo* (i.e. 1.56 instead of 1.58). Thus the correction factors for the common dwell times in clinical practice (20 min or more), as presented in this study for the sigmoid tonometer, are also applicable to the gastric tonometer. Further, carbon dioxide remaining in the deadspace saline after each aspiration can influence subsequent measurements by pushing, upon reintroduction of saline, some carbon dioxide-containing saline into the balloon and increasing starting Pi_{CO_2},[24] resulting in overestimation of Pi_{CO_2} of 10% and 6% at dwell times of 10 and 20 min, respectively. Rinsing of the tonometer four times before each reintroduction of saline circumvents this effect.[24] We took this phenomenon into account, thereby explaining a similar goodness of fit of model 2 for the *in vivo* as for the *in vitro* data.

There is large variation in calculated normal Pi_{CO_2} and pHi between centres, and our study suggests that this may be from differences and errors in methodology (table 4). For example, in many studies, information on the blood-gas analyser, dwell time used, or both, was not provided.[10 15 23 25 26 29 30] The saline method has been compared with the recently developed automated, semicontinuous air tonometry, an apparently simple and reliable technique that may circumvent many of the methodological problems associated with manual saline tonometry *in vitro* and in critically ill patients.[23 28–30] In contrast with this method, Pco_2 measured by saline tonometry and corrected for dwell time may overestimate surrounding P_{CO_2}, particularly at short dwell times. This overestimation may be from high correction factors for short dwell times provided by the manufacturer, erroneously incorporating bias of the blood-gas analyser.[23 28] In comparing saline with air tonometry *in vivo*,[23 29 30] however, fair agreement was observed, but since blood-gas analyser bias was not reported, it cannot be judged how the normal saline tonometric variables used as a gold standard were obtained. The correction factors and normal values for saline

Table 4 Effects of tonometer type, manufacturer's dwell time-dependent correction factors, and blood-gas analyser bias on expected Pi_{CO_2}. Expected Pi_{CO_2} was caculated using our *in vivo* correction factors (table 1) supplemented by our blood-gas analyser bias of 15%

Dwell time (min)	Sigmoid/Gastric type correction factor of the manufacturer	% Difference from expected Pi_{CO_2}: Without correction/ for blood-gas analyser bias of −15%	/ −7%	With correction for blood gas analyser bias of −15%
10	1.57/1.62	−16%/−13%	−8%/−5%	−1%/+3%
20	1.39/1.36	−9%/−11%	0%/−2%	+8%/+6%
30	1.29/1.24	−8%/−12%	+1%/−3%	+8%/+4%
45	1.19/1.16	−11%/−13%	−2%/−5%	+5%/+3%
60	1.17/1.13	−9%/−13%	−1%/−5%	+7%/+3%
120	1.17/1.11	−5%/−10%	+4%/−2%	+12%/+6%

tonometry reported in this study may, in turn, form a reference base for future evaluation of other types of tonometry *in vivo*.

It may be questioned if Pi_{CO_2} increase in healthy volunteers applies to critically ill patients. Critically ill patients may have mucosal hypoperfusion, oedema and swelling, which may slow transmucosal $P\text{CO}_2$ diffusion and tonometer Pi_{CO_2} increase. Limitation of intramucosal diffusion may not adversely effect Pi_{CO_2} increase in the tonometer balloon, however, if it is true that the latter is mainly determined by luminal rather than mucosal $P\text{CO}_2$.[33] In fact, gastric aqueous contents approximate 40 ml after suppression of acid secretion and consist of mucus covering gastric mucosa and free secretions.[33] Complete equilibration of a 2.5-ml balloon would decrease gastric fluid and mucus $P\text{CO}_2$ by 6% (or 0.3 kPa), and therefore hardly any transmucosal diffusion is needed to offset Pi_{CO_2} build-up in the tonometer balloon.

Finally, the idea that Pi_{CO_2} is partly dependent on $P\text{CO}_2$ in blood supplying the gastric mucosa,[6] is supported by the relationship between the two variables in our study, even in the relatively narrow blood $P\text{CO}_2$ range in healthy subjects. Our results indicate that the normal gastric mucosal $P\text{CO}_2$ depends on alveolar ventilation, if blood flow is adequate. As changes in arterial $P\text{CO}_2$ may affect Pi_{CO_2} in a similar direction, the difference in $P\text{CO}_2$ between gastric lumen and arterial blood is more likely to constitute a sensitive and specific measure for the adequacy of mucosal blood flow than Pi_{CO_2} and pHi per se, that do not incorporate blood $P\text{CO}_2$.[6] Further, pHi is confounded by arterial blood bicarbonate content, that may vary independently from mucosal bicarbonate content.[6] Therefore, we supplied normal values for Pi_{CO_2}–pHi and blood $P\text{CO}_2$–pH differences in addition to those for Pi_{CO_2} and pHi alone.

In summary, we have provided, for the first time, valid and measurement bias-independent correction factors and normal values for variables obtained by manual saline tonometry in the human stomach. The study may improve comparability of results among centres and may widen the clinical acceptance of the technique.

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References

1. Montgomery A, Hartman M, Jonsson K, Haglund U. Intramucosal pH measurement with tonometers for detecting gastrointestinal ischemia in porcine hemorrhagic shock. *Circulatory Shock* 1989; **29**: 319–327.
2. Antonsson JB, Boyle CC, Kruithoff KL, Wang HL, Sacristan E, Rothschild HR, Fink MP. Validation of tonometric measurement of gut intramural pH during endotoxemia and mesenteric occlusion in pigs. *American Journal of Physiology* 1990; **259**: G519–G523.
3. Noc M, Weil MH, Sun S, Gazmuri RJ, Tang W, Pakula JL. Comparison of gastric luminal and gastric wall $P\text{CO}_2$ during hemorrhagic shock. *Circulatory Shock* 1993; **40**: 194–199.
4. Tang W, Weil MH, Sun S, Noc M, Gazmuri RH, Bisera J. Gastric intramural $P\text{CO}_2$ as monitor of perfusion failure during hemorrhagic and anaphylactic shock. *Journal of Applied Physiology* 1994; **76**: 572–577.
5. Kolkman JJ, Groeneveld ABJ, Meuwissen SGM. Effect of ranitidine on basal and bicarbonate enhanced intragastric $P\text{CO}_2$: A tonometric study. *Gut* 1994; **35**: 737–741.
6. Groeneveld ABJ, Kolkman JJ Splanchnic tonometry: A review of physiology, methodology, and clinical applications. *Journal of Critical Care* 1994; **9**: 198–210.
7. Parviainen I, Vaisänen O, Ruokonen E, Takala J. Effect of nasogastric suction and ranitidine on the calculated gastric intramucosal pH. *Intensive Care Medicine* 1996; **22**: 319–323.
8. Schlichtig R, Bowles SA. Distinguishing between aerobic and anaerobic appearance of dissolved CO_2 in intestine during low flow. *Journal of Applied Physiology* 1994; **76**: 2443–2451.
9. Desai VS, Weil MH, Tang WC, Yang G, Bisera J. Gastric intramural $P\text{CO}_2$ during peritonitis and shock. *Chest* 1993; **104**: 1254–1258.
10. Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. *Critical Care Medicine* 1987; **15**: 153–156.
11. Doglio GR, Pusajo JF, Egurrola MA, Bonfigli GC, Parra C, Vetere L, Hernandez MS, Fernandez S, Palizas F, Gutierrez G. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Critical Care Medicine* 1991; **19**: 1037–1040.
12. Marik PE. Gastric intramucosal pH—a better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. *Chest* 1993; **104**: 225–229.
13. Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. *Intensive Care Medicine* 1994; **20**: 99–104.
14. Roumen RMH, Vreugde JPC, Goris RJA. Gastric tonometry in multiple trauma patients. *Journal of Trauma* 1994; **36**: 313–316.
15. Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi E, Jorge M, Pusajo J, Klein F, San Roman E, Dorfman B, Shottlender J, Giniger R. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; **339**: 195–199.
16. Gutierrez G, Clark C, Brown SD, Price K, Ortiz L, Nelson C. Effect of dobutamine on oxygen consumption and gastric intramucosal pH in septic patients. *American Journal of Respiratory and Critical Care Medicine* 1994; **150**: 324–329.
17. Fiddian-Green RG, Amelin PM, Herrmann JB, Arous E, Cutler BS, Schiedler M, Wheeler HB, Baker S. Prediction of the development of sigmoid ischemia on the day of aortic operations. *Archives of Surgery* 1986; **121**: 654–660.
18. Tonometrics. Sigmoid tonomitor. *Comprehensive Sigmoid Tonomitor Instructions* (ST V1.3), 1989.
19. Takala J, Parviainen I, Siloaho M, Ruokonen E, Hämalainen E. Saline $P\text{CO}_2$ is an important source of error in the assessment of gastric intramucosal pH. *Critical Care Medicine* 1994; **22**: 1877–1879.
20. Riddington D, Vankatesh KB, Clutton-Brock T, Bion J. Measuring carbon dioxide tension in saline and alternative solutions: quantification of bias and precision in two blood gas analyzers. *Critical Care Medicine* 1994; **22**: 96–100.
21. Knichwitz G, Mertes N, Kuhmann M. Improved $P\text{CO}_2$ measurement in six standard blood gas analysers using a phosphate-buffered solution for gastric tonometry. *Anaesthesia* 1995; **50**: 532–534.
22. Kolkman JJ, Zwarekant LJ, Boshuizen K, Steverink PGHM, Groeneveld ABJ, Meuwissen SGM. Type of solution and $P\text{CO}_2$ measurement errors during tonometry. *Intensive Care Medicine* 1997; **23**: 658–663.
23. Creteur J, De Backer D, Vincent JL. Monitoring gastric mucosal carbon dioxide pressure using gas tonometry. *Anesthesiology* 1997; **87**: 504–510.
24. Steverink PJGM, Kolkman JJ, Groeneveld ABJ, De Vries JW. Catheter dead space: a source of error during tonometry. *British Journal of Anaesthesia* 1998; **80**: 337–341.
25. Diebel L, Kozol R, Wilson RF, Mahajan S, Abuhamdan D, Thomas D. Gastric intramucosal acidosis in patients with chronic kidney failure. *Surgery* 1993; **113**: 520–526.
26. Andersen LW, Landow L, Baek L, Jansen E, Baker S. Association between gastric intramucosal pH and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor-alpha concentrations in patients undergoing cardiopulmonary bypass. *Critical Care Medicine* 1993; **21**: 210–217.
27. Smithies M, Yee TH, Jackson L, Beale R, Bihari D. Protecting the gut and the liver in the critically ill: effects of dopexamine. *Critical Care Medicine* 1994; **22**: 789–795.

28. Kolkman JJ, Zwarekant LJ, Boshuizen K, Groeneveld ABJ, Meuwissen SGM. In vitro evaluation of intragastric $P\mathrm{co}_2$ measurement by air tonometry. *Journal of Clinical Monitoring* 1997; **13**: 115–119.
29. Heinonen PO, Jousela IT, Blomqvist KA, Olkkola KT, Takkunen OS. Validation of air tonometric measurement of gastric regional concentrations of CO_2 in critically ill septic patients. *Intensive Care Medicine* 1997; **23**: 524–529.
30. Taylor DE, Gutierrez G, Hainley S. Measurement of gastric mucosal carbon dioxide tension by saline and air tonometry. *Journal of Critical Care* 1997; **12**: 208–213.
31. Stokkel LA, Klinkenberg-Knol EC, Breedijk M. Microcomputer system for long-term ambulatory pH recording. *Medical and Biological Engineering and Computing* 1987; **25**: 107–109.
32. Dar K, Williams T, Aitken R, Woods KL, Fletcher S Arterial versus capillary sampling for analysing blood gas pressures. *British Medical Journal* 1995; **310**: 24–25.
33. Kolkman JJ, Groeneveld ABJ, Meuwissen SGM. Gastric $P\mathrm{co}_2$ tonometry is independent of carbonic anhydrase inhibition. *Digestive Diseases and Sciences* 1997; **42**: 99–102

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Gastric tonometry: *in vivo* comparison of saline and air tonometry in patients with cardiogenic shock

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Summary

Measurement of gastric intramucosal pH (pHi) has been advocated to assess gastric perfusion. Regional $P\text{co}_2$ (r$P\text{co}_2$) values are measured using saline tonometry (rs$P\text{co}_2$) and more recently using air tonometry (ra$P\text{co}_2$). We compared 237 measurements of saline and air tonometry in 19 consecutive, severely ill patients (mean age 59 (range 31–76) yr, 19 males, APACHE II 22±7) with cardiogenic shock. Equilibration period was set to 90 min. Nineteen independent paired samples of mean ra$P\text{co}_2$ and mean rs$P\text{co}_2$ of each patient showed good correlation (r=0.93, P<0.001). Mean ra$P\text{co}_2$ was 6.5 (1.8) kPa and mean rs$P\text{co}_2$ 6.8 (2.4) kPa. $P\text{co}_2$ measured by saline was significantly higher than that measured by air (P<0.05). Bland and Altman analysis showed a bias (mean rs$P\text{co}_2$–mean ra$P\text{co}_2$) of 0.3 kPa and a precision of 1.2 kPa. Agreement between the two methods decreased with increasing r$P\text{co}_2$ concentrations. Although air tonometry of r$P\text{co}_2$ is a promising technique, a systematic disagreement with saline tonometry at high r$P\text{co}_2$ values requires further investigation and cautious interpretation of these values. (*Br. J. Anaesth.* 1998; **81**: 676–680).

Keywords. gastrointestinal tract, mucosal perfusion; gastrointestinal tract, pH; measurement techniques, tonometry

Gastric tonometry for estimation of intramucosal pH (pHi) in severely ill patients is becoming increasingly used in intensive care units. Low pHi is thought to indicate gastrointestinal ischaemia, identifying those patients at risk of developing complications attributable to mucosal disruption in critical illness. Determination of pHi has been used to guide treatment of critically ill patients[1] and as a measure of outcome prediction.[2] The value of pHi in the mucosa is obtained indirectly by measuring the regional partial pressure of carbon dioxide (r$P\text{co}_2$) in the lumen of the stomach with a saline-filled silicone balloon tonometer and the bicarbonate (HCO_3^-) concentration in arterial blood, and substituting these two values in the Henderson–Hasselbalch equation.[3] It is assumed that the HCO_3^- concentration in the intracellular fluid of the tissue is in equilibrium with the HCO_3^- concentration in mucosal capillary blood which is further presumed to be the concentration found in blood.[4]

Until recently r$P\text{co}_2$ was determined by analysing saline from the tonometer balloon, a method suggested to be a source of several errors. Depending on design features of the blood-gas analyser, varying amounts of carbon dioxide are lost from the sample because of the low stability of carbon dioxide in saline before carbon dioxide analysis by the carbon dioxide electrode is completed.[5] Differences in blood-gas analysers which indicate different $P\text{co}_2$ values from identical samples may contribute to erroneous intramucosal pH values.[5,6] Further, tonometry does not allow rapid assessment of r$P\text{co}_2$. Because of these concerns a continuous air tonometric monitoring system was developed.

In this study, we have compared the (semi-) automatic air tonometry method with conventional saline tonometry in critically ill patients in terms of accuracy and precision.

Patients and methods

The study was approved by the local Ethics Committee of the University Hospital of Aachen and conducted according to the principles of the Helsinki Declaration.

We studied prospectively 19 consecutive patients (mean age 59 (31–76) yr, 19 males, APACHE II 22 ± 7) admitted to the cardiology intensive care unit of the University Hospital of Aachen with cardiogenic shock. All patients were sedated and underwent mechanical ventilation. Therefore, informed consent was obtained from the closest relatives. Cardiogenic shock was caused by anterior myocardial infarction in 10 of 19 patients, posterior myocardial infarction in four of 19 patients, ischaemic cardiomyopathy in four of 19 patients and dilated cardiomyopathy in one patient. Eleven of the 19 patients (58%) died. Haemodynamic values of all patients before study entry are shown in table 1. No patient received enteral nutrition and famotidine 20 mg (Pepdul, MSD Chibropharm, München, Germany) was administered i.v. twice daily.

Two gastric tonometer catheters (TRIP NGS catheter, Tonometric Division, Instrumentarium, Helsinki, Finland) were placed in the stomach via the nasogastric route. Correct placement of the tubes was verified radiologically. Measurements of r$P\text{co}_2$ were performed 90, 180 and 270 min after entry to the study and thereafter three times daily with saline (rs$P\text{co}_2$) and air (ra$P\text{co}_2$) tonometry. The equilibration period was 90 min for each measurement. The end of study was defined as removal of gastric

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Table 1 Haemodynamic data (mean (SD)) of 19 patients with cardiogenic shock before study entry. PCWP=Pulmonary capillary wedge pressure

Variable	
Cardiac index (litre min^{-1} m^{-2})	1.63 (0.27)
Heart rate ($beat^{-1}$ min)	126 (17)
Systolic arterial pressure (mm Hg)	90 (11)
Mean arterial pressure (mm Hg)	62 (7)
Diastolic arterial pressure (mm Hg)	48 (7)
PCWP (mm Hg)	20 (4)

tonometers for clinical reasons (e.g. extubation) or if death occurred. Arterial blood-gas analysis was carried out simultaneously using a standard blood-gas analyser (ABL 505 blood gas analyser, Radiometer, Copenhagen, Denmark).

An automated gas analyser (Tonocap TC 200, Tonometric Division, Instrumentarium, Helsinki, Finland) was connected to one of the gastric tonometer catheters. This monitor supplies the tonometer balloon with room air. The gas is held in the catheter balloon for a set period of time for diffusion to take place. This equilibration period may be predefined (10, 15, 30 or 60 min) or is set manually. With each measurement cycle, 6 ml of air are pumped into the balloon. A sample is then obtained automatically after the selected cycle period. The first 1.2 ml, equivalent to the deadspace of the system, are discarded. $P\mathrm{co}_2$ is measured in the remainder with an infrared sensor. Using an internal nafion tube (used in the Tonocap) water vapour partial pressure of the probe equilibrates with the environmental water vapour partial pressure. The technology of the Tonocap in respect to management of different water vapour partial pressures is comparable with the standard technique applied in other systems, such as capnography, where carbon dioxide is determined by infrared absorbance.

pHi is calculated from arterial pH (pHa), arterial $P\mathrm{co}_2$ (Pa_{CO_2}) and ra$P\mathrm{co}_2$:

$$\mathrm{pHi}=\mathrm{pHa}+\log_{10}(Pa_{\mathrm{CO}_2}/\mathrm{raPsco}_2)$$

The second tonometer balloon was primed following the manufacture's guidelines and filled with 2.5 ml of 0.9% saline. After 90 min of equilibration, anaerobic samples of the tonometer saline were obtained, discarding the deadspace volume of 1 ml. The saline samples were handled in capped syringes to avoid or minimize any possible equilibration with room air. All samples were analysed immediately and discarded if a delay during the sample process occurred. rs$P\mathrm{co}_2$ was determined using the same blood-gas analyser as for arterial blood-gas analysis, and pHi was calculated:

$$\mathrm{pHi}=6.1+\log_{10}(\text{arterial } \mathrm{HCO}_3^-/1.12\times0.03\times \mathrm{rs}P\mathrm{co}_2$$

The term 1.12 is a time-dependent equilibration factor from *in vitro* studies where the tonometer was exposed for ≥90 min to a physiological saline solution with a known $P\mathrm{co}_2$, and "0.03" is the solubility coefficient of carbon dioxide in saline.

Arterial HCO_3^- is calculated by the blood-gas analyser:

$$\mathrm{HCO}_3^-=0.23\times Pa_{\mathrm{CO}_2}\times\mathrm{antilog}(\mathrm{pH}-\mathrm{pK});$$
$$\mathrm{pK}=6.125-\log_{10}(1+\mathrm{antilog}(\mathrm{pH}-8.7)$$

All probes were analysed by the blood-gas analyser at 37°C and thereafter corrected for the patient's actual body temperature using internal software because $P\mathrm{co}_2$ in a saline sample which is kept anaerobic changes with temperature; the equation used for internal temperature correction, according to the manufacturer's handbook was:

$$P\mathrm{co}_2(\mathrm{temp})=P\mathrm{co}_2(37^\circ\mathrm{C})\times10^{0.021\times(\mathrm{temp}-37^\circ\mathrm{C})}$$

Statistical analysis was with a microcomputer using the Statistical Package for the Social Sciences (SPSS, SPSS Inc., Chicago, IL, USA). All data are given as mean (SD). The Wilcoxon signed rank test and Pearson's correlation coefficient were performed with pooled data. Simple linear regression analysis was applied to each patient's mean rs$P\mathrm{co}_2$ and ra$P\mathrm{co}_2$ values. Agreement between saline samples and Tonocap measurements were analysed according to the method of Bland and Altman.[7] Bias is the mean difference between rs$P\mathrm{co}_2$ and ra$P\mathrm{co}_2$ and precision the SD of the differences.

Results

We obtained 237 paired samples (table 2). Mean duration of tonometry was 77 (49) h. We did not observe any complication associated with the two tonometer probes (e.g. nasopharyngeal injuries, oesophageal or gastric bleeding). Mean air $P\mathrm{co}_2$ was 6.5 (1.8) kPa and mean saline $P\mathrm{co}_2$ 6.8 (2.4) kPa.

There were no negative $P\mathrm{co}_2$ differences in either saline tonometry (rs$P\mathrm{co}_2$–Pa_{CO_2}=2.3 (2.3) kPa) or in air tonometry (ra$P\mathrm{co}_2$–Pa_{CO_2}=1.9 (1.6) kPa). $P\mathrm{co}_2$ values from both methods were highly correlated ($n=19$, Pearson's $r=0.93$; $P<0.0001$ (two-tailed)). Figure 1 shows regression analysis of each patients's mean ra$P\mathrm{co}_2$ and rs$P\mathrm{co}_2$ values. $P\mathrm{co}_2$ measured by saline tonometry was significantly higher than that from the Tonocap ($P<0.05$ (two-tailed)). Mean pHi calculated from the Tonocap was 7.29 (0.11) while with the saline method it was 7.20 (0.12). A Bland and Altman plot showed a bias of 0.3 kPa and a precision of 1.2 kPa (fig. 2).

Agreement between the two methods decreased at greater r$P\mathrm{co}_2$ values. Using an arbitrary difference of 7.3 kPa, paired samples with rs$P\mathrm{co}_2$ values greater than 7.3 kPa had a bias of 1.2 kPa and a precision of 1.8 kPa. Below 7.3 kPa, bias was –0.04 kPa and precision was 0.7 kPa (fig. 3).

Table 2 Pooled data of 237 paired samples of air tonometry (ra$P\mathrm{co}_2$) and saline tonometry (rs$P\mathrm{co}_2$). Pa_{CO_2}=arterial carbon dioxide, rs$P\mathrm{co}_2$–Pa_{CO_2}=carbon dioxide difference between regional carbon dioxide obtained by saline tonometry and arterial carbon dioxide, ra$P\mathrm{co}_2$–Pa_{CO_2}=carbon dioxide difference between regional carbon dioxide obtained by air tonometry and arterial carbon dioxide

Variable	
Pa_{CO_2} (kPa)	4.7 (0.7)
HCO_3^- (mmol $litre^{-1}$)	22.2 (3.2)
Arterial pH	7.42 (0.05)
rs$P\mathrm{co}_2$ (kPa)	6.8 (2.4)
ra$P\mathrm{co}_2$ (kPa)	6.5 (1.8)
$\mathrm{pHi}_{\mathrm{saline}}$	7.20 (0.12)
$\mathrm{pHi}_{\mathrm{air}}$	7.29 (0.11)
rs$P\mathrm{co}_2$–Pa_{CO_2} (kPa)	2.3 (2.3)
ra$P\mathrm{co}_2$–Pa_{CO_2} (kPa)	1.9 (1.6)

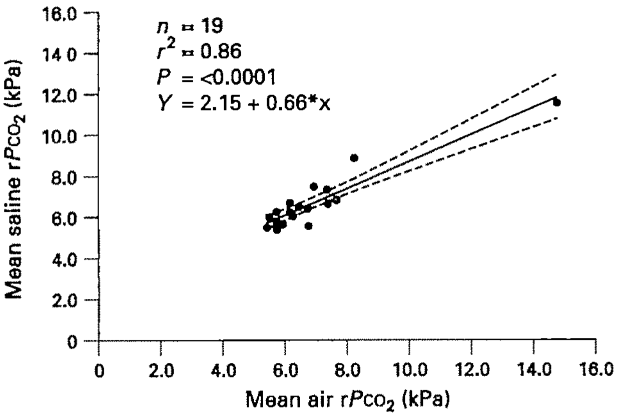

Figure 1 Scatter plot showing relationship between mean regional $P\text{CO}_2$ ($rP\text{CO}_2$) obtained by air tonometry ($raP\text{CO}_2$) and saline tonometry ($rsP\text{CO}_2$) in 19 patients. Solid line=regression line; broken line=95% confidence interval around the regression line. r^2=coefficient of determination.

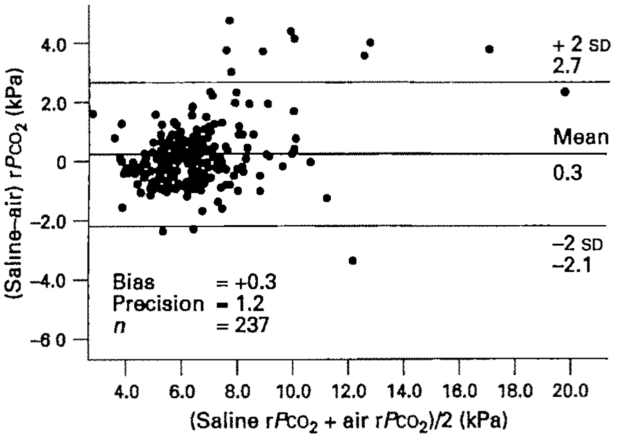

Figure 2 Bland and Altman analysis of regional $P\text{CO}_2$ ($rP\text{CO}_2$) obtained by air tonometry ($raP\text{CO}_2$) and saline tonometry ($rsP\text{CO}_2$) with a 90-min cycle time. Bias=mean difference between $rsP\text{CO}_2$ and $raP\text{CO}_2$ and precision=SD of the differences. n=Number of paired samples

Discussion

Indirect estimation of gut wall intramucosal pH was popularized by the work of Fiddian-Green and co-workers who promoted this technique for the early detection of splanchnic ischaemia.[8-10] Tonometry has been proposed to predict mortality and morbidity,[2 10-12] provide a target in goal-directed therapy[1] and to gauge therapeutic efficacy on splanchnic perfusion.[13-15] Nevertheless, it remains a research method rather than a routine technique in the critically ill patient.

Until recently, tonometry was performed using 0.9% saline. Several authors have suggested the potential hazards, namely underestimation of $P\text{CO}_2$ by different blood-gas analysers and hence overestimation of pHi.[6 16] This bias is caused by a low stability of carbon dioxide in saline. Thus different constructions of blood-gas analysers can cause different carbon dioxide losses from the sample before it reaches the measuring electrode.[5] The ABL 505 blood-gas analyser, which was used in our study, gives only minor underestimation of saline $P\text{CO}_2$ after equilibration with different gas mixtures compared with five other systems.[5] Substituting a phosphate-buffered[5 17] or colloid[18] solution for saline may improve $P\text{CO}_2$ measurements in blood-gas analysers. However, the higher carbon dioxide-binding capacity of the buffer prolongs the equilibration time between tissue and sample carbon dioxide. Therefore, the ability of the saline method to detect rapid changes in regional carbon dioxide is not improved and remains a problem.

Moreover, saline tonometry is subject to several errors from variation in sample handling and time delay.[19] The development of air tonometry provides the clinician with a feasible technique without the aforementioned limitations.

In our study, saline and air tonometry showed a good correlation. We chose a cycle time of 90 min to ensure a steady state between $P\text{CO}_2$ in the mucosa and in the saline filled tonometer balloon. To ensure comparability, the cycle time of the Tonocap device was set to 90 min also, although an equilibration time of 10 min may be sufficient for air tonometry.[20 21] Saline tonometry seems to overestimate $rP\text{CO}_2$ after an equilibration period of 90 min as shown by the bias of 0.3 kPa. So far there are no data on $rP\text{CO}_2$ values obtained by saline tonometry commensurable with air tonometry at 90 min. Creteur, De Backer and Vincent found a bias of 0.5 kPa in 84 paired measurements at 30 min[20] and Heinonen and colleagues found a bias of 0.2 kPa in a small number of 14 paired $rP\text{CO}_2$ determinations at 60 min.[21] Overestimation of $rP\text{CO}_2$ by saline in our study was attributable predominantly to 61 measurements of high $rP\text{CO}_2$ values greater than 7.3 kPa (fig. 3A, B), which were detected in 16 of 19 patients. Excluding these values, a small bias of –0.04 kPa with an acceptable precision of 0.7 kPa were found. Therefore, high regional $P\text{CO}_2$ concentrations are subject to inappropriate overestimation by saline tonometry.

In vitro air tonometry with the Tonocap, performed in a gas chamber fully saturated with five different carbon dioxide concentrations, showed comparable $P\text{CO}_2$ values except for the first 10-min cycle,[21] but these authors did not give bias and precision values from their *in vitro* experiments. Recently, Creteur, De Backer and Vincent reported on their *in vitro* validation studies for air and saline tonometry.[20] For an equilibration time of 10 min at a water bath $P\text{CO}_2$ concentration of 5.3 kPa, air tonometry gave a bias of –0.04 kPa and a precision of 0.09 kPa, whereas bias and precision of saline tonometry were –0.9 kPa and 0.4 kPa, respectively. Increasing the equilibration time of the Tonocap did not improve the precision or decrease the bias.[20] Their *in vitro* experiments further support the conclusion that equilibration times of 30 min cannot be recommended for saline tonometry. Thirty minutes after increasing the water bath $P\text{CO}_2$ concentration from 5.3 to 10.7 kPa, $P\text{CO}_2$ measured by saline and air tonometry was 7.3 (0.3) kPa and 10.8 (0.1) kPa, respectively. Taken together with our results, comparison of both methods at different cycle times must be interpreted with caution. Equilibration periods of less than 30 min inevitably underestimate $rP\text{CO}_2$ determined by saline tonometry. Moreover, long cycle times ≥90 min may fail to detect rapid changes in $rP\text{CO}_2$ by saline tonometry. As yet there is no explanation for overestimation of $rP\text{CO}_2$ by saline tonometry compared with air tonometry at high $rP\text{CO}_2$ concentrations. Neglecting high saline $rP\text{CO}_2$ values eliminated this presumed error in

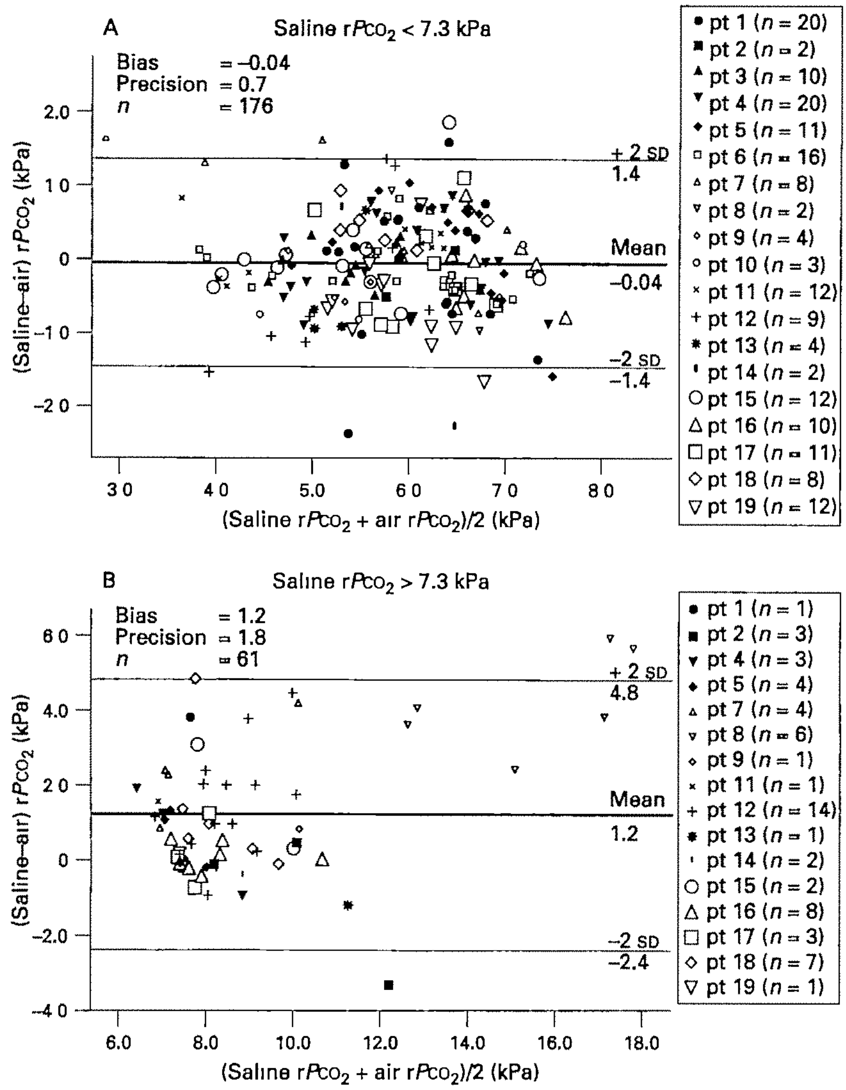

Figure 3 Bland and Altman analysis of regional $P\text{CO}_2$ ($rP\text{CO}_2$) obtained by air tonometry ($raP\text{CO}_2$) and saline tonometry ($rsP\text{CO}_2$) with a 90-min cycle time for 19 patients divided into paired samples with $rsP\text{CO}_2$ greater than 7 3 kPa (A) and less than 7 3 kPa (B), respectively Note that individual patient points are displayed separately and number of measurements per patient (*n*) are displayed. Bias=mean difference between $raP\text{CO}_2$ and $rsP\text{CO}_2$ and precision=SD of the differences. *n*=Number of paired samples

measurement (fig. 3). Further *in vitro* studies should aim to elucidate this discrepancy between the methods at high $rP\text{CO}_2$ levels.

There are no published data on differences between the behaviour of saline and blood in blood-gas analysers at different temperatures. Although we corrected $P\text{CO}_2$ for patient temperature using the internal software of the blood-gas analyser, it should be emphasized that the equation provided by the manufacturer does not apply directly to saline, and may result in a systematic error.

When computing pHi from $rsP\text{CO}_2$ and $raP\text{CO}_2$, mean pHi showed a mean difference of 0.09 although mean $rsP\text{CO}_2$ differed by only 0.3 kPa from mean $rsP\text{CO}_2$. This is mainly attributable to the two different formulae applied for calculation pHi. Saline tonometry uses arterial HCO3_3^- which is calculated automatically by the blood-gas analyser from arterial pH and Pa_{CO_2}, whereas air tonometry computes pHi making use of arterial pH and Pa_{CO_2}. Further, the equilibration time dependent factor and the solubility coefficient in the saline tonometry equation may add to a systematic bias in computing pHi by both methods thus causing a higher pHi calculated using air tonometry. Assuming equal $rP\text{CO}_2$ concentrations measured by saline and air tonometry and a constant equilibration time in saline tonometry, the difference in pHi is governed exclusively by arterial pH and may range from 0.06 at a given arterial pH of 6.8, to 0.03 at a given arterial pH of 7.6

Our study population consisted of severely ill patients in cardiogenic shock with a mortality of 58%. Concordantly pooled data of $rP\text{CO}_2$–Pa_{CO_2} difference as an index of gut ischaemia were remarkably high (table 2) suggesting severe local tissue dysoxia. We did not assess $rP\text{CO}_2$ and pHi as predictors of morbidity and mortality in our investigation. However, several studies have shown that pHi values have prognostic value after both cardiac and major vascular surgery and also in general critical care patients.[2 11 12 22 23] Normal values for pHi and the $rP\text{CO}_2$–Pa_{CO_2} difference have not been established so far. Air tonometry offers potential measurement of $P\text{CO}_2$ values with less sources of errors than saline tonometry, and may allow early recognition of splanchnic ischaemia. Future research may focus on this method to assess $rP\text{CO}_2$, pHi and $rP\text{CO}_2$–Pa_{CO_2} indices of gastric oxygenation and predictors of mortality. Furthermore, therapeutic interventions to improve oxygen delivery may be judged more quickly and accurately than that with saline tonometry.

In summary, we found a good correlation between air tonometry and saline tonometry. Overestimation of r$P\mathrm{co}_2$ at high regional carbon dioxide concentrations by saline tonometry compared with air tonometry remains unexplained and requires (*in vitro*) further investigation. Air tonometry may become the standard means of assessing r$P\mathrm{co}_2$. Discrepancies from saline tonometry, particularly at high $P\mathrm{co}_2$ concentrations, should lead the clinician to interpret these values with caution.

References

1. Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi E, Jorge M, Pusajo J. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; **339**: 195–199.
2. Doglio G, Pusajo J, Egurrola M, Bonfigli G, Gutierrez G. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Critical Care Medicine* 1991; **19**: 1037–1040.
3. Fiddian-Green RG. Gastric intramucosal pH, tissue oxygenation and acid–base balance. *British Journal of Anaesthesia* 1995; **74**: 591–606.
4. Arnold J, Hendriks J, Ince C, Bruining H. Tonometry to assess the adequacy of splanchnic oxygenation in the critically ill patient. *Intensive Care Medicine* 1994; **20**: 452–456.
5. Knichwitz G, Mertes N, Kuhmann M. Improved PCO_2 measurement in six standard blood gas analysers using a phosphate-buffered solution for gastric tonometry. *Anaesthesia* 1995; **50**: 532–534.
6. Riddington D, Venkatesh B, Clutton-Brock T, Bion J. Potential hazards in estimation of gastric intramucosal pH. *Lancet* 1992; **340**: 547.
7. Bland JM, Altman DG. Statistical method for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i**: 307–310.
8. Fiddian-Green RG, McGough E, Pittenger G, Rothman E. Predictive value of intramural pH and other risk factors for massive bleeding from stress ulceration. *Gastroenterology* 1983; **85**: 613–620.
9. Fiddian-Green RG, Pittenger G, Whitehouse WMJ. Back-diffusion of CO_2 and its influence on the intramural pH in gastric mucosa. *Journal of Surgical Resuscitation* 1982; **33**: 39–48.
10. Fiddian-Green RG, Amelin PM, Herrmann JB, Arous E, Cutler BS, Schiedler M, Wheeler HB, Baker S. Prediction of the development of sigmoid ischemia on the day of aortic operations. Indirect measurements of intramural pH in the colon. *Archives of Surgery* 1986; **121**: 654–660.
11. Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: Comparison with other monitoring. *Critical Care Medicine* 1987; **15**: 153–156.
12. Gutierrez G, Bismar H, Dantzker DR, Silva N. Comparison of gastric intramucosal pH with measures of oxygen transport and consumption in critically ill patients. *Critical Care Medicine* 1992; **20**: 451–457.
13. Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *Journal of the American Medical Association* 1994; **272**: 1354–1357
14. Gardeback M, Settergren G. Dopexamine and dopamine in the prevention of low gastric mucosal pH following cardiopulmonary by-pass. *Acta Anaesthesiologica Scandinavica* 1995; **39**.1066–1070.
15. Trinder TJ, Lavery GG, Fee JP, Lowry KG. Correction of splanchnic oxygen deficit in the intensive care unit: dopexamine and colloid versus placebo. *Anaesthesia in Intensive Care* 1995; **23**: 178–182.
16. Takala J, Parviainen I, Siloaho M, Ruokonen E, Hämäläinen E. Saline $P\mathrm{co}_2$ is an important source of error in the assessment of gastric intramucosal pH. *Critical Care Medicine* 1994; **22**: 1877–1879.
17. Eichelbronner O, Feist H, Georgieff M, Radermacher P. Reliability of tonometric intramucosal PCO_2 measurement with a phosphate-buffer solution. *Intensive Care Medicine* 1995; **21**: 387–388.
18. Riddington D, Venkatesh B, Clutton Brock T, Bion J, Venkatesh KB. Measuring carbon dioxide tension in saline and alternative solutions: quantification of bias and precision in two blood gas analyzers. *Critical Care Medicine* 1994; **22**: 96–100.
19. Wood PR, Cudworth P, Davies GE, Lawler PG. Potential hazards in estimation of gastric intramucosal pH. *Lancet* 1992; **340**: 913–913.
20. Creteur J, De Backer D, Vincent J-L. Monitoring gastric mucosal carbon dioxide pressure using gas tonometry: in vitro and in vivo validation studies. *Anesthesiology* 1997; **87**: 504–510.
21 Heinonen PO, Jousela IT, Blomqvist KA, Olkkola KT, Takkunen OS. Validation of air tonometric measurement of gastric regional concentrations of CO_2 in critically ill septic patients. *Intensive Care Medicine* 1997; **23**: 524–529.
22. Sutcliffe NP, Mostafa SM. pHi: a review of the literature. *Clinical Intensive Care* 1996; **7**: 258–264.
23. Mythen MG, Purdy G, Mackie IJ, McNally T, Webb AR, Machin SJ. Postoperative multiple organ dysfunction syndrome associated with gut mucosal hypoperfusion, increased neutrophil degranulation and C1-esterase inhibitor depletion. *British Journal of Anaesthesia* 1993; **71**: 858–863.

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Airway closure, atelectasis and gas exchange during general anaesthesia†

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Summary

Airway closure and the formation of atelectasis have been proposed as important contributors to impairment of gas exchange during general anaesthesia. We have elucidated the relationships between each of these two mechanisms and gas exchange. We studied 35 adults with healthy lungs, undergoing elective surgery. Airway closure was measured using the foreign gas bolus technique, atelectasis was estimated by analysis of computed x-ray tomography, and ventilation–perfusion distribution ($\dot{V}_A/\dot{Q}$) was assessed by the multiple inert gas elimination technique. The difference between closing volume and expiratory reserve volume (CV–ERV) increased from the awake to the anaesthetized state. Linear correlations were found between atelectasis and shunt (r=0.68, P<0.001), and between CV–ERV and the amount of perfusion to poorly ventilated lung units ("low $\dot{V}_A/\dot{Q}$", r=0.57, P=0.001). Taken together, the amount of atelectasis and airway closure may explain 75% of the deterioration in Pa_{O_2}. There was no significant correlation between CV–ERV and atelectasis. We conclude that in anaesthetized adults with healthy lungs, undergoing mechanical ventilation, both airway closure and atelectasis contributed to impairment of gas exchange. Atelectasis and airway closure do not seem to be closely related. (*Br. J. Anaesth.* 1998; **81**: 681–686).

Keywords: anaesthesia, general; airway, pressure; lung, atelectasis; lung, gas exchange; ventilation, ventilation–perfusion

Impairment of gas exchange during general anaesthesia with mechanical ventilation is a well known finding.[1 2] In several recent investigations, the formation of atelectasis with subsequent pulmonary shunting was shown to be related to impairment of gas exchange.[3 4] In addition to shunt, ventilation–perfusion ($\dot{V}_A/\dot{Q}$) mismatch and perfusion to lung units with poor ventilation in relation to their respective perfusion ("low $\dot{V}_A/\dot{Q}$") have been demonstrated during anaesthesia.[4] This low $\dot{V}_A/\dot{Q}$ increases with age.[4] Thus poorly ventilated lung units contribute more to impairment of gas exchange in older patients compared with younger ones. The cause of low $\dot{V}_A/\dot{Q}$ is not clear. One possibility is airway closure. It was demonstrated initially in awake subjects[5] and has been shown to increase in magnitude with age.[6 7] It has also been shown in anaesthetized subjects,[8–11] but its extent and influence on gas exchange have not been fully agreed upon. Airway closure occurs during deep expiration, beginning in the dependent lung regions. If closure (or marked narrowing, see also below) of airways occurs during a normal breath (i.e. above functional residual capacity), ventilation in affected lung regions is impaired, and this should result in a $\dot{V}_A/\dot{Q}$ mismatch with low $\dot{V}_A/\dot{Q}$. By combining measurements of airway closure, atelectasis and $\dot{V}_A/\dot{Q}$ distribution, further insight into the mechanisms of impairment of gas exchange may be obtained.

Therefore, in this study, we have elucidated the relationships between airway closure, atelectasis, $\dot{V}_A/\dot{Q}$ distribution and impaired oxygenation during general anaesthesia with mechanical ventilation.

Patients and methods

A total of 35 patients were included in the study (table 1). Another 14 patients refused to participate (i.e. refusal rate of 29%). No patient had cardiac or pulmonary disease on the basis of history and clinical examination. Some data from the same patients (concerning atelectasis and gas exchange) have been presented previously.[12–14] The study was approved by the Ethics Committee of the University Hospital of Uppsala, Sweden and informed consent was obtained from each subject.

In awake patients, measurements were obtained with the subject lying supine on the CT table and breathing air. Computed tomography of the lungs was performed, and ventilation–perfusion distribution and airway closure were measured. Anaesthesia was induced, and all measurements were repeated after a minimum of 20 min of anaesthesia (see below). Finally, the patient was moved from the x-ray department to the operating theatre to undergo surgery.

Details of the anaesthetic have been described previously.[12–14] Before induction, all patients received atropine 0.5 mg i.v. Anaesthesia was induced with fentanyl 1–2 μg kg^{-1} and propofol 2 mg kg^{-1} i.v.,

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Table 1 Patient characteristics (mean (SD)), median [range] or number). BMI= Body mass index calculated as weight×height^{-2}

	Mean (SD)	Median [range]
Sex (M/F)	20/15	
Non-smoker/smoker	30/5	
Age (yr)	45 (11)	48 [19–66]
Weight (kg)	79 (14)	79 [53–103]
Height (cm)	173 (8.6)	175 [160–195]
BMI (kg m^{-2})	26.0 (3.5)	26.3 [18.3–33.2]

followed by a continuous infusion of propofol 4–8 mg kg^{-1} h^{-1}. The dose of these drugs was adjusted according to clinical signs of depth of anaesthesia (arterial pressure and heart rate). During induction, the lungs were ventilated manually via a face mask with 100% oxygen. To facilitate orotracheal intubation, patients received pancuronium 0.1 mg kg^{-1}; additional doses of 1–2 mg were given when needed. The lungs were ventilated mechanically at a rate of 10 bpm with 40% oxygen in nitrogen (Servo Ventilator 900C, Siemens Elema AB, Solna, Sweden). No positive end-expiratory pressure was used. Tidal volume was adjusted to maintain an end-tidal carbon dioxide concentration of approximately 4% (CO_2 analyser Eliza, Datex-Engström, Helsinki, Finland). The resulting tidal volume was 9±1 ml kg^{-1}.

The electrocardiogram, arterial pressure (Riva-Rocci method) and peripheral arterial oxygen saturation (pulse oximetry: Biox 3740, Ohmeda, Louisville CO, USA) were monitored throughout the study.

CLOSING VOLUME

Closing volume (CV) was measured using the foreign gas bolus technique, with helium as the tracer gas.[5 6] A specially designed device, including a Fleisch pneumotachograph, flow-integrator, and helium dosing and measuring unit was used (Hebotest Godart, Einthoven, Netherlands). Details of this equipment have been described previously.[15] With the conscious, supine subject breathing air, spirometry values of a few normal breaths were recorded first. Starting from maximal expiration (residual volume, RV) the subject was asked to inspire maximally until vital capacity (VC). During the initial phase of this inspiration, a bolus dose (300 ml) of helium was added to the inspired gas. During the subsequent expiration, the concentration of helium in the expired gas was plotted against expired volume on an X–Y recorder (Model 50000, Bryans, Mitcham, UK). Both maximal inspiration and expiration were made at a rate of approximately 0.5 litre s^{-1}. The onset of phase IV on the helium concentration curve was taken as onset of airway closure, and the volume expired during phase IV to RV was defined as CV. Note that CV–ERV (expiratory reserve volume) is the volume above functional residual capacity (FRC) where airway closure starts (see also comments on methodology below). If CV–ERV is a negative number, onset of airway closure is below FRC. Two or more measurements were made to obtain a minimum of two acceptable curves (even flow during inspiration and expiration, inspired and expired volume equal within 5%).

In the anaesthetized subject, a 7 L syringe was used for manual ventilation of the lungs during measurements. The lungs were deflated to an airway pressure (*P*aw) of −15 cm H_2O, a level considered to reflect RV. After automatic injection of the helium bolus, the lungs were inflated to a *P*aw of 40 cm H_2O and immediately deflated at a constant flow rate of approximately 0.5 litre s^{-1} to RV. *P*aw was measured using a manometer (BOC Ohmeda, Louisville CO, USA) attached to the tracheal tube. Inflation up to 40 cm H_2O was taken to represent total lung capacity and VC was taken as the volume between this inflation and the assumed RV. Further analysis of CV was performed analogous to the procedure in awake subjects.

The mean of 2–3 readings of ERV, CV and VC were used for further statistical analysis. CV was expressed as volume (ml) and as percentage of expired VC (%VC).[16] To test if the reproducibility of the CV measurement was affected by recruitment of atelectasis by the VC manoeuvre, the difference between the first and subsequent measurements of airway closure during general anaesthesia were compared with the amount of atelectasis. Only patients with more than 5 cm^2 of atelectasis (see below) were included in this analysis.

Further, the predicted VC (dependent on age, sex and height) for awake subjects was calculated according to Cotes.[17]

COMPUTED TOMOGRAPHY OF THE LUNGS

Atelectasis was studied by computed x-ray tomography (Somatom plus, Siemens, München, Germany) and has been described previously.[12 18] Subjects were in the supine position with their arms above the head. A frontal scout view, covering the chest, and a CT scan in the transverse plane, 1 cm above the top of the right diaphragm, were obtained at end-expiration (FRC), in the awake subject and after induction of anaesthesia. Scan time was 1 s, and slice thickness was 8 mm. With a matrix of 512x512, the resulting picture element (pixel) was approximately 1.5x1.5 mm.

To identify atelectasis, a magnified image of the dorsal portion of the CT scan of both the right and left lung was made. The dorsal border between the thoracic wall and the dense areas was drawn manually, whereas the ventral border between inflated lung tissue and atelectasis was identified by the region-of-interest (ROI) program. All pixels with attenuation values between −100 and +100 Hounsfield units (HU) were considered to represent atelectatic lung tissue.[18] For the logarithmic transformation (see results below), the smallest possible value of atelectasis was assumed to be 0.1 cm^2. This value represents the smallest amount that can reasonably be measured by CT.

VENTILATION–PERFUSION DISTRIBUTION AND BLOOD-GAS ANALYSIS

Ventilation–perfusion distribution ($\dot{V}A/\dot{Q}$) was assessed using the multiple inert gas elimination technique.[19 20] This method is based on the elimination and retention of a number of "inert" gases (usually six). Because pulmonary artery catheters were not acceptable for this study, a simplified method was applied, with measurements of inert gases in arterial blood and mixed expired air.[21] Using the Fick principle, cardiac output was estimated from oxygen con-

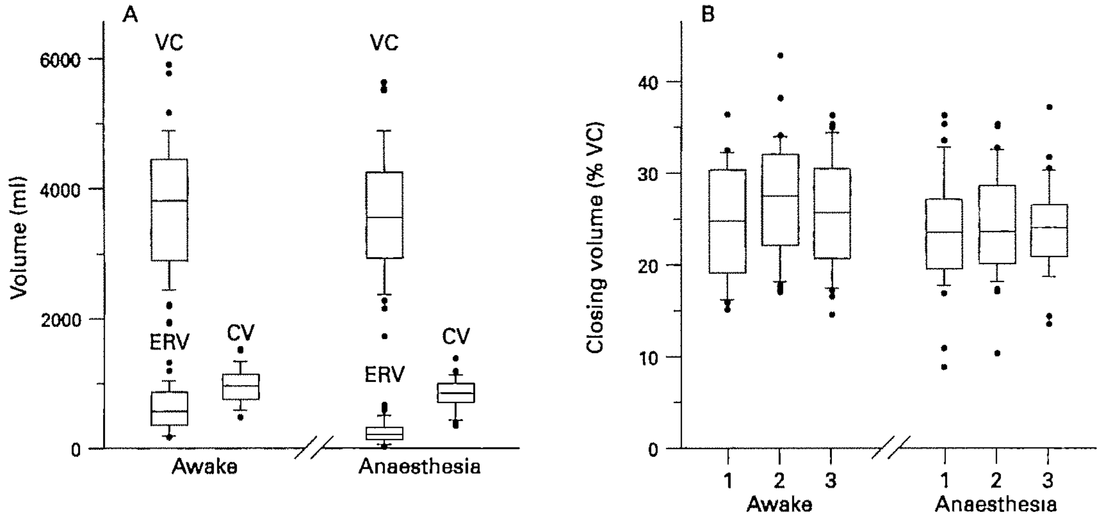

Figure 1 Box and whisker plots of lung volume measurements in awake and anaesthetized subjects. The box indicates the range between the 25th and 75th percentiles, the line marks the 50th percentile. Capped bars (whiskers) indicate the 10th and 90th percentiles and data outside these bars are shown as dots. For details on measurements, see text. A. VC=vital capacity, ERV=expiratory reserve volume and CV=closing volume. B: Consecutive measurements of CV (%VC) in awake and anaesthetized, supine subjects. Note that there was no difference between the first and third measurements, either awake or during anaesthesia.

sumption, assuming an arteriovenous oxygen content difference of 50 ml litre^{-1} blood,[14] and mixed venous inert gas concentrations were then computed using mass balance principles.[22] Approximation of cardiac output was imprecise but it has been shown that indices of $\dot{V}A/\dot{Q}$ mismatch remain essentially unaffected by such uncertainties.[22] Further, shunt and low $\dot{V}A/\dot{Q}$ may be estimated with reasonable accuracy.[14]

In brief, isotonic saline with a mixture of six inert gases (sulphur hexafluoride, ethane, cyclopropane, enflurane, diethyl ether and acetone) was infused continuously into a peripheral vein. Under steady state conditions, arterial blood and mixed expired gas samples were collected in duplicate for subsequent analysis by gas chromatography (Hewlett Packard Gas Chromatograph 5880A and 5890, Palo Alto CA, USA). By mathematical analysis of the inert gas data, each $\dot{V}A/\dot{Q}$ distribution was recovered in a 50-compartment model and the result with the best fit of data (smallest remaining sum of squares, RSS) of each pair of duplicate samples was used for further statistical analysis. Intrapulmonary shunt was defined as the fraction of total blood flow perfusing lung units with $\dot{V}A/\dot{Q}$ <0.005, and low $\dot{V}A/\dot{Q}$ (=lung units with poor ventilation in relation to their perfusion) was defined as the fraction of total blood perfusion to lung units with $0.005<\dot{V}A/\dot{Q}<0.1$. Log SDQ was calculated as the SD value of the logarithmic distribution of perfusion. This value is a measure of dispersion of blood flow distribution.

Blood-gas measurements were performed using a standard technique (ABL 300 Radiometer, Copenhagen, Denmark).

STATISTICAL ANALYSIS

Unless otherwise stated, mean (SD) values are presented. In addition, 95% confidence intervals (95% CI) are given where appropriate. To compare data between awake and anaesthetized subjects, the paired sample *t* test was used. The Pearson correlation coefficient was used to describe relationships between two different variables. To analyse relationships between more than two variables, a stepwise multiple linear regression with analysis of residuals was performed. For all calculations, the SYSTAT 5.0 computer software package (SYSTAT, Evanston IL, USA) was used.

Table 2 Lung volume measurement, computed tomography of the lungs and gas exchange (mean (SD)) (see text for details). VC=Vital capacity; CV=closing volume, ERV=expiratory reserve volume; Atelectasis=dense areas (−100 to +100 HU), measured in a transverse CT scan at the dome of the right diaphragm; Thoracic area=cross-sectional chest area, measured in the same scan as atelectasis (for details see text); $F\text{I}_{O_2}$=fraction of inspired oxygen; Pa_{O_2}, Pa_{CO_2}=arterial partial pressure of oxygen and carbon dioxide, respectively; Shunt=$\dot{V}A/Q<0.005$; low $\dot{V}A/Q=0.005<\dot{V}A/Q<0.1$, log SDQ=SD of logarithmic distribution of perfusion; COest.=estimated cardiac output (see text)

	Awake	Anaesthetized	*P*
VC (ml)	3800 (1010)	3680 (1010)	0.2
ERV (ml)	650 (390)	300 (210)	< 0.001
CV (ml)	980 (290)	870 (260)	0.034
CV (%VC)	25.9 (5.6)	24.1 (5.3)	0.09
CV–ERV (ml)	330 (410)	570 (290)	0.002
Atelectasis (cm2)	0.0 (0.0)	7.1 (6.6)	< 0.001
Thoracic area (cm2)	347 (63)	325 (56)	< 0.001
$F\text{I}_{O_2}$	0.21	0.40	—
Pa_{O_2} (kPa)	12.5 (2.2)	19.8 (6.9)	—
Pa_{CO_2} (kPa)	5.2 (0.8)	4.5 (0.3)	< 0.001
Shunt (% COest.)	0.1 (0.5)	6.5 (5.1)	< 0.001
Low $\dot{V}A/Q$ (%COest.)	2.3 (3.3)	5.4 (8.7)	0.016
Log SDQ	0.76 (0.32)	1.08 (0.30)	< 0.001
COest. (litre min^{-1})	4.8 (1.1)	3.8 (0.9)	< 0.001

Results

AWAKE

In awake, supine subjects, VC was 3800 (1010) ml. This corresponds to 89 (17) % of the predicted VC in sitting subjects.[17] There was no significant difference between the first and succeeding measurements of CV (fig. 1, right). Mean CV was 980 (290) ml or 25.9 (5.6) % VC. The difference between CV and ERV (CV–ERV) was 330 (410) ml (range −1080 to 910 ml) (table 2, fig. 1, left).

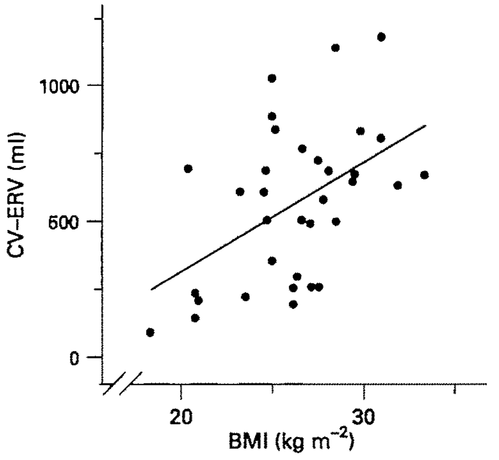

Figure 2 Body constitution and airway closure during general anaesthesia with mechanical ventilation. BMI=Body mass index, a measure of body constitution. CV–ERV=closing volume–expiratory reserve volume. A linear regression line is shown: CV–ERV (ml)=–490+41xBMI (kg m^{-2}); r=0.49, P=0.003.

CT scans revealed no atelectasis or other lung pathology. Data on gas exchange and ventilation–perfusion distribution are given in table 2.

GENERAL ANAESTHESIA

Airway closure and atelectasis

Mean VC in anaesthetized subjects was 3680 (1010) ml (fig. 1, left). This is equivalent to 98 (14) % of VC while awake. There was no increase in CV from the first to the second and third measurements (fig. 1, right). Mean CV was 870 (260) ml or 24.1 (5.3) % VC, and mean CV–ERV was 570 (290) ml (range 90–1190 ml). Compared with awake, CV–ERV increased by 250 (440) ml (95% CI 100–410 ml, P=0.002) (table 2).

The relationship between airway closure and body constitution (BMI) is presented in figure 2. The characteristics of the linear regression between airway closure and age are given in table 3.

Table 3 Correlation coefficients of linear regressions between two variables during general anaesthesia (for definitions, see text)

Variable			r	P
Age	*vs*	CV %VC	0.38	0.024
Age	*vs*	Log SDQ	0.45	0.008
CV–ERV	*vs*	Atelectasis	0.32	0.092
CV–ERV	*vs*	Low $\dot{V}A/\dot{Q}$	0.57	0.001
CV–ERV	*vs*	Shunt + low $\dot{V}A/\dot{Q}$	0.63	< 0.001
CV–ERV	*vs*	Log SDQ	0.51	0.003
Atelectasis	*vs*	Shunt	0.68	< 0.001

The mean amount of atelectasis at the base of the lungs was 7.1 (6.6) cm^2 (mean and 95% CI, calculated after logarithmic transformation: 3.4–1.9–6.2 cm^2). There was no correlation between airway closure and atelectasis (table 3).

Ventilation–perfusion distribution and Pa_{O_2}

Data on ventilation–perfusion distribution and oxygenation of arterial blood are given in table 2. There was a correlation between pulmonary shunt and atelectasis (fig. 3, left) and between airway closure (expressed as CV–ERV) and low $\dot{V}A/\dot{Q}$ (table 3, fig. 3, right). The correlation coefficient r was slightly greater when total perfusion to lung units with either poor or no ventilation (low $\dot{V}A/\dot{Q}$+shunt) was related to airway closure (table 3).

A linear correlation was found between Pa_{O_2} on the one hand and shunt and perfusion to poorly ventilated lung units (low $\dot{V}A/\dot{Q}$) on the other (r=0.94, P<0.001). There also was a linear correlation between Pa_{O_2} and airway closure (r=0.59, P<0.001). Adding atelectasis as a further variable to this analysis gave a greater correlation coefficient and therefore an increased coefficient of determination (r^2):

$$Pa_{O_2}\ (\text{kPa})=29-2.9\times\ln\ (\text{atelectasis}\ (\text{cm}^2))$$
$$-0.0085\ (\text{CV–ERV}\ (\text{ml}));\ r=0.86,\ P<0.001.$$

where Pa_{O_2}=arterial partial pressure of oxygen, measured at FI_{O_2}=0.40, and ln (atelectasis)=natural logarithm of atelectasis.

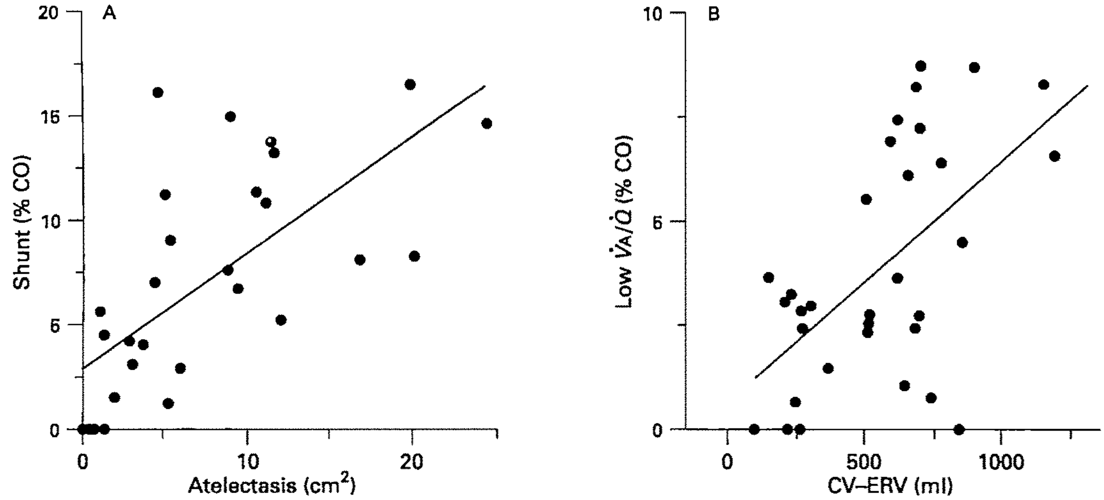

Figure 3 A. Atelectasis and shunt during general anaesthesia with mechanical ventilation. Atelectasis=amount of densities (+100 to −100 HU) in a CT scan 1 cm above the dome of the right diaphragm (cm^2); shunt=perfusion to lung units with 0.005<$\dot{V}A/Q$< 0.1; CO=cardiac output. A linear regression line is shown: shunt (% CO)=2.9+0.55xatelectasis (cm^2); r=0.68, P<0.001. B: Airway closure and ventilation–perfusion distribution mismatch during general anaesthesia with mechanical ventilation. CV–ERV (see fig. 2), low $\dot{V}A/Q$=perfusion to lung units with 0.005<$\dot{V}A/Q$< 0.1; CO=cardiac output. A linear regression line is shown: low $\dot{V}A/Q$ (% CO)= 0.68+0.006x(CV–ERV (ml)); r=0.57, P=0.001.

Finally, Pa_{O_2} was also related to age and body constitution (BMI), resulting in the following equation:

Pa_{O_2} (kPa)=53–0.16×age (yr)–1.0xBMI (kg m^{-2}) r=0.61, P=0.001.

Discussion

We have shown that impaired oxygenation during uneventful anaesthesia in patients with healthy lungs can be explained by shunt and perfusion to units with poor ventilation in relation to their perfusion ("low $\dot{V}A/\dot{Q}$"). The results also suggest that airway closure is a likely mechanism of low $\dot{V}A/\dot{Q}$ during anaesthesia. Atelectasis is associated with shunt, as proposed in earlier investigations[3 4] and confirmed in this study. Together, atelectasis and airway closure can explain 75% of the impairment of arterial oxygenation.[1]

COMMENTS ON METHODOLOGY

Measurements of lung volumes, both in awake and anaesthetized subjects, yielded results similar to previous investigations.[8 16] The difference from predicted VC in the awake subject[17] may be explained by differences in body position (supine *vs* sitting).

Estimation of airway closure is based on either a resident gas technique (nitrogen washout) or a foreign gas bolus technique. A steep increase in the gas concentration at the end of expiration from VC (termed onset of phase IV) is considered to indicate an abrupt increase in the amount of airway closure in dependent regions of the lung.[5] Accordingly, the volume above RV at which phase IV begins is termed CV. Despite the fact that the term "airway closure" might suggest a single clearly defined event, it should be remembered that a certain amount of airway closure may exist before the onset of phase IV.[23] Further, a marked increase in airway resistance[24 25] or flow limitation[23] may contribute to the onset of phase IV. Despite these limitations, strong evidence exists for the occurrence of true airway closure, although it may not be the sole mechanism responsible for the onset of phase IV (for a detailed review see Rehder[26]).

For measurement of airway closure in anaesthetized subjects, the foreign gas bolus technique is more appropriate than the nitrogen washout technique because of less dependency on the vertical lung volume gradient[16] and on variations in the inspiratory manoeuvre.[27] Further, rapid onset of absorption atelectasis[14] may interfere with CV measurements if the VC manoeuvre is performed with 100% oxygen, as used in the nitrogen washout technique. In our investigation, using the foreign gas (helium) bolus technique and room air for the VC manoeuvre, there was no obvious relationship between amount of atelectasis and variability between the two or three measurements of CV during general anaesthesia. This agrees with the finding that previously collapsed lung tissue is reopened within the first few seconds of a VC manoeuvre (Neumann and colleagues, unpublished observations) and with the fact that most of the re-expanded lung tissue remains aerated for more than 40 min if air is used for the VC manoeuvre and if the lungs are ventilated with 40% oxygen in nitrogen thereafter.[15] Lung tissue, re-opened during the initial phase of the first measurement procedure, is accessible and thus is included during all subsequent measurements of airway closure.

AIRWAY CLOSURE

The significant increase in airway closure (expressed as CV–ERV) from awake to anaesthesia confirms earlier investigations,[9 16] but some studies found no difference in CV–ERV between the awake state and anaesthesia.[10] Appropriate explanations for these different results are lacking.

In anaesthetized subjects, there was a correlation between airway closure (CV–ERV) and body constitution, expressed as body mass index (BMI). Obese patients tended to have more airway closure during anaesthesia, and airway closure was greater in older patients, which is similar to findings in conscious subjects.[7]

AIRWAY CLOSURE, ATELECTASIS AND GAS EXCHANGE

Pulmonary shunt was greater in anaesthetized subjects whose airway closure (although measured while awake) occurred above FRC.[28] Our data, with both variables measured in anaesthetized subjects, did not confirm such a close relationship between shunt and airway closure. However, there was a significant linear correlation between airway closure (expressed as CV–ERV) and low $\dot{V}A/\dot{Q}$. Subjects with a larger CV above ERV (CV–ERV) had greater perfusion to poorly ventilated lung units. There also was a linear correlation between airway closure and other measures of ventilation–perfusion distribution mismatch (log SDQ or low $\dot{V}A/\dot{Q}$+shunt). These findings suggest that airway closure may reflect a major part of lung units subject to severe ventilation–perfusion mismatch.

A correlation between airway closure and Pa_{O_2} during general anaesthesia has been found previously.[8 11] These investigations concluded that airway closure contributed to pulmonary dysfunction, but may not be the most important mechanism.[11] This was confirmed by our investigation. Thus the more airway closure, the worse the oxygenation of arterial blood. Adding atelectasis to the linear regression equation markedly increased the correlation coefficient. Our data showed that 75% of the variation in Pa_{O_2} was accounted for by atelectasis and airway closure.[29] If one considers the many other factors (e.g. cardiac output, oxygen consumption) that may influence Pa_{O_2}, this agreement is quite high. Therefore, we conclude that both atelectasis and airway closure are important determinants and may explain most of the impairment of gas exchange during general anaesthesia in patients with healthy lungs undergoing mechanical ventilation.

Based on the above findings, the "ideal patient", with no atelectasis and no airway closure during normal tidal breathing, will have an estimated Pa_{O_2} of 36 kPa at an FI_{O_2} of 0.4. This hypothetical value is in accordance with that described recently for subjects with no shunt and no $\dot{V}A/\dot{Q}$ mismatch.[30]

In summary, in adults with healthy lungs, both airway closure and atelectasis contributed to impairment of gas exchange during general i.v. anaesthesia with mechanical ventilation. There was a close relationship between airway closure and disturbance of ventilation–perfusion distribution. Atelectasis and shunt impaired gas exchange, but the amount of atelectasis did not appear to be related closely to the amount of airway closure. Impairment of gas exchange was more pronounced in older and obese patients.

Acknowledgements

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References

1. Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. *New England Journal of Medicine* 1963; **269**: 991–996.
2. Nunn JF, Bergman NA, Coleman AJ, Jones DD. Factors influencing the arterial oxygen tension during anaethesia with artificial ventilation. *British Journal of Anaesthesia* 1965, **37**: 898–914.
3. Brismar B, Hedenstierna G, Lundquist H, Strandberg Å, Svensson L, Tokics L. Pulmonary densities during anesthesia with muscular relaxation—a proposal of atelectasis. *Anesthesiology* 1985; **62**: 422–428
4. Gunnarsson L, Tokics L, Gustavsson H, Hedenstierna G. Influence of age on atelectasis formation and gas exchange impairment during general anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 423–432.
5. Milic-Emili J, Henderson JAM, Dolovich MB, Trop D, Kaneko K. Regional distribution of inspired gas in the lung. *Journal of Applied Physiology* 1966; **21**: 749–759.
6. Anthonisen NR, Danson J, Robertson PC, Ross WRD. Airway closure as a function of age. *Respiration Physiology* 1969/70; **8**: 58–65.
7. Leblanc P, Ruff F, Milic-Emili J. Effects of age and body position on "airway closure" in man. *Journal of Applied Physiology* 1970; **28**: 448–451.
8. Hedenstierna G, McCarthy G, Bergström M. Airway closure during mechanical ventilation. *Anesthesiology* 1976; **44**: 114–123.
9. Gilmour I, Burnham M, Craig DB. Closing capacity measurement during general anesthesia. *Anesthesiology* 1976; **45**: 477–482.
10. Juno P, Marsh HM, Knopp TJ, Rheder K. Closing capacity in awake and anesthetized–paralyzed man. *Journal of Applied Physiology* 1978; **44**: 238–244.
11. Bergman NA, Tien YK. Contribution of the closure of pulmonary units to impaired oxygenation during anesthesia. *Anesthesiology* 1983; **59**: 395–401.
12. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G. Re-expansion of atelectasis during general anaesthesia: a computed tomography study. *British Journal of Anaesthesia* 1993, **71**: 788–795.
13. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G. Reexpansion of atelectasis during general anaesthesia may have a prolonged effect. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 118–125.
14. Rothen HU, Sporre B, Engberg G, Wegenius G, Högman M, Hedenstierna G. Influence of gas composition on recurrence of atelectasis after a reexpansion maneuver during general anesthesia. *Anesthesiology* 1995; **82**: 832–842.
15. Hedenstierna G, Alexandersson R, Kolmodin-Hedman B, Szamosi A, Tollqvist J. Pleural plaques and lung function in construction workers exposed to asbestos. *European Journal of Respiratory Diseases* 1981, **62**: 111–122.
16. Hedenstierna G, Santesson J. Airway closure during anesthesia: a comparison between resident-gas and argon-bolus techniques. *Journal of Applied Physiology* 1979; **47**: 874–881.
17. Cotes JE. *Lung Function*, 4th Edn. Oxford: Blackwell Scientific Publications, 1979.
18. Lundquist H, Hedenstierna G, Strandbereg Å, Tokics L, Brismar B. CT-assessment of dependent lung densities in man during general anaesthesia. *Acta Radiologica* 1995; **36**: 626–632.
19. Wagner PD, Saltzman HA, West JB Measurement of continuous distributions of ventilation–perfusion ratios: theory. *Journal of Applied Physiology* 1974; **36**: 588–599.
20. Wagner PD, Laravuso RB, Uhl RR, West JB Continuous distributions of ventilation–perfusion ratios in normal subjects breathing air and 100% O_2. *Journal of Clinical Investigation* 1974; **54**: 54–68.
21. Wagner PD, Hedenstierna G, Bylin G, Lagerstrand L. Reproducibility of the multiple inert gas elimination technique. *Journal of Applied Physiology* 1987; **62**: 1740–1746.
22. Wagner PD, Smith CM, Davies NJH, McEvoy RD, Gale GE. Estimation of ventilation–perfusion inequality by inert gas elimination without arterial sampling. *Journal of Applied Physiology* 1985; **59**: 376–383.
23. Forkert L, Dhingra S, Anthonisen NR Airway closure and closing volume. *Journal of Applied Physiology* 1979; **46**: 24–30.
24. Rodarte JR, Hyatt RE, Cortese DA Influence of expiratory flow on closing capacity at low expiratory flow rates. *Journal of Applied Physiology* 1975; **39**: 60–65.
25. Lehane JR, Jordan C, Jones JG. Influence of halothane and enflurane on respiratory airflow resistance and specific conductance in anaesthetized man. *British Journal of Anaesthesia* 1980; **52**: 773–781.
26. Rehder K, Marsh HM, Rodarte JR, Hyatt RE. Airway closure. *Anesthesiology* 1977, **47**: 40–52.
27. Holtz B, Bake B, Oxhoj H. Effect of inspired volume on closing volume. *Journal of Applied Physiology* 1976; **41**: 623–630.
28. Dueck R, Prutow RJ, Davies NJH, Clausen JL, Davidson TM. The lung volume at which shunting occurs with inhalation anesthesia. *Anesthesiology* 1988; **69**: 854–861.
29. Dawson-Saunders B, Trapp RG. *Basic and Clinical Biostatistics*. East Norwalk, Connecticut: Appleton and Lange, 1990; 54–57.
30. Petros AJ, Doré CJ, Nunn JF. Modification of the iso-shunt lines for low inspired oxygen concentrations. *British Journal of Anaesthesia* 1994; **72**: 515–522.

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Correlating fibreoptic nasotracheal endoscopy performance and psychomotor aptitude

A. K. DASHFIELD AND J. E. SMITH

Summary

We have investigated the correlation between the scores attained on computerized psychometric tests, measuring psychomotor and information processing aptitudes, and learning fibreoptic endoscopy with the videoendoscope. Sixteen anaesthetic trainees performed two adaptive tracking tasks (ADTRACK 2 and ADTRACK 3) and one information management task (MAZE) from the MICROPAT testing system. They then embarked on a standardized fibreoptic training programme during which they performed 15 supervised fibreoptic nasotracheal intubations on anaesthetized oral surgery patients. There was a significant correlation between the means of the 15 endoscopy times and both ADTRACK 2 ($r=-0.599$, $P=0.014$) and ADTRACK 3 ($r=-0.589$, $P=0.016$) scores. The correlation between the means of the 15 endoscopy times and MAZE scores was not significant. The ratios of the mean endoscopy time for the last seven endoscopies to the mean endoscopy time for the first seven endoscopies were not significantly correlated with ADTRACK 2, ADTRACK 3 or MAZE scores. Psychomotor abilities appeared to be determinants of trainees' initial proficiency in endoscopy, but did not appear to be determinants of trainees' rates of progress during early fibreoptic training. (*Br. J. Anaesth.* 1998; **81**: 687–691).

Keywords: intubation nasotracheal; intubation nasotracheal, training; anaesthetists, training; equipment, fibreoptic laryngoscope

Perceptual–motor skills involve the combination of perceptual, cognitive and motor abilities in a closed-loop system.[1] First, sensory information is detected and assembled and passed on to the information processing stage. Here, decisions about appropriate responses are made and a motor programme is organized. This programme is effected by the motor system and the resulting action generates response feedback which presents further sensory information for evaluation.

Much psychological research has been directed towards the objective assessment of perceptual–motor abilities.[2] Abilities are inherited, stable and enduring aptitudes that an individual brings to the performance of his life tasks. There may be up to 50 specific perceptual–motor abilities,[1 3] such as spatial orientation, information comprehension, manual dexterity, etc. All individuals have all the abilities, but different individuals have different patterns of strengths and weaknesses in their abilities, as defined by their genetic make-up. Skill describes an individual's proficiency at a particular task that has developed with and is modified by practice. An individual may acquire countless skills but each particular skill is based on a specific combination of the relatively small number of fundamental abilities. Thus abilities underlie and are limiting factors of the individual's skilled performance of a task.[1 3]

Microprocessor-controlled neuropsychological or psychometric tests have been developed to measure a range of perceptual–motor abilities. Psychometric tests may be classified according to the type of perceptual–motor ability they examine, for example perception, information management or psychomotor, although often there are no clear-cut distinctions and there is much overlapping.[4] Many psychometric tests have been validated as reliable predictors of technical skill performance and they appear to have practical applications in personnel recruitment in many spheres of everyday life.[5] In the Armed Services, batteries of psychometric tests, in conjunction with personality questionnaires, curriculum vitae analyses and formal interviews are used to select candidates who are likely to be successful in pilot training.[6 7] Psychomotor tests, for example adaptive tracking tasks, which measure eye–hand co-ordination, are particularly relevant here, but increasingly, as flying systems become more complex and aircrews need to monitor and control computer-based systems, information management ability is also expedient. In the UK, a fully automated selection testing system, MICROPAT (MICROcomputerized Personnel Aptitude Tester), which assesses both psychomotor and information management ability patterns, has been developed and validated.[4 7]

In the field of anaesthesia, learning fibreoptic endoscopy demands that anaesthetists develop new types of practical skills.[8] It may be that eye–hand co-ordination and other psychomotor abilities are among the primary aptitudes on which flexible endoscopy skills are based. However, there is no information on whether psychometric test scores can predict endoscopy skills. In this study, we have investigated if there were significant correlations between the scores obtained by anaesthetic trainees on MICROPAT psychomotor and information management tests and the times taken for the trainees to perform their first 15 fibreoptic nasotracheal endoscopies.

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Subjects and methods

The study was approved by the South Birmingham Local Research Ethics Committee. Sixteen consecutive anaesthetic trainees appointed to the Birmingham School of Anaesthesia who had no previous experience in fibreoptic techniques performed three computerized psychometric tests, ADTRACK 2 (AD2), ADTRACK 3 (AD3) and MAZE from the MICROPAT testing system.[7] The anaesthetic trainees were tested in the morning, having not been on duty the night before. Normal caffeine ingestion and tobacco consumption were allowed before psychometric testing and during fibreoptic training, as the training programme often took many days to complete and it may have been impractical to restrict the intake of these items during the whole of this period. None of the trainees were computer game enthusiasts. The trainees performed the MICROPAT tests with their dominant hand controlling the joystick (and they similarly held the fibrescope controls in the dominant hand when they embarked on the fibreoptic training programme).

AD2 and AD3 are joystick-controlled, one-dimensional adaptive pursuit tracking tasks designed to test eye–hand co-ordination. Adaptive refers to the task becoming more difficult as the candidate's performance improves. In AD2, the computer displayed a block surrounded by two bars. The computer moved the bars from side to side and the trainee was required to keep the block as close to the bars as possible using the joystick. A number on the screen told the candidate how well he or she was doing. The lowest possible score was 1 and the highest, 17. AD3 is similar to AD2 except that the trainee could control the adaptation. The screen showed the current difficulty level and an indication of the amount of error in performance at that level. Difficulty level or adaptation was increased by pressing one key and decreased by pressing another. The adaptation increased automatically in AD2 and AD3 by speeding up the pursuit. In AD3, difficulty level could be increased further by making the trajectory less predictable.

MAZE was designed to test information management abilities. Candidates were required to direct nine separate targets around a square maze on the computer screen until they reached the middle (home). The targets moved in straight lines and the operator had to tell them to turn corners by pushing a button. The targets set off at equally timed intervals, so that it was possible to have nine targets requiring direction at any one time. If a target failed to turn a corner and "crashed", then that target was lost. The final score was calculated on the overall distance travelled by the targets. Full instructions were displayed on the screen for all tests so that no intervention by an instructor was required. Typical time for instructions, practice and testing for each of the three tests was 10 min. To avoid any possibility of bias, neither instructors nor trainees were made aware of any psychometric scores—all test data were stored on the computer hard disk and no scores were compiled until all trainees had completed their fibreoptic training programmes.

Each anaesthetic trainee then embarked on a standardized graduated fibreoptic training programme, described previously.[9] Initially, the set-up of the videoendoscope system was demonstrated to the trainee, as were the fibrescope controls and the correct way to manipulate the instrument. Trainees then had a structured, video-controlled practice session on a bronchial tree model, after which they viewed a videotape recording showing details of airway anatomy and good endoscopy technique. Each trainee then performed 15 fibreoptic nasotracheal endoscopies and intubations with the videoendoscope under the supervision of an experienced trainer. Patients were ASA I or II, aged 16–70 yr, undergoing elective oral surgery requiring nasotracheal intubation.

Trainees were required to perform fibreoscopy only in patients who were expected to present uncomplicated fibreoptic intubations. Hence patients were not obese, had no history of oesophageal reflux, no evidence of nasal obstruction and no significant abnormality of the airway. Electrocardiogram, indirect arterial pressure, arterial oxygen saturation and carbon dioxide concentrations were monitored and patients' lungs were preoxygenated. Anaesthesia comprised glycopyrrolate, fentanyl, propofol and atracurium. The patient's lungs were hyperventilated with isoflurane in oxygen using a face mask attached to a Bain breathing system, after which endoscopy was conducted in a standard manner. The trainee performed endoscopic anterior rhinoscopy in both nostrils, selected the most patent, moved the fibrescope forward either underneath or alongside the inferior turbinate, identified structures in the nasopharynx, then advanced the instrument through the pharynx, larynx and trachea to the carina. Finally, the tracheal tube was railroaded over the fibrescope which guided it into the trachea to complete the intubation. The importance of continually seeing the airway and identification of airway anatomy was emphasized. The instructor gave demonstrations, advice, feedback guidance and assistance as necessary. Videotape recordings of the first five endoscopies were made following General Medical Council guidelines, and were subsequently reviewed by trainee and instructor during a debriefing session. Endoscopy time was taken as the time required to move the fibrescope from the first nostril examined to the carina and was recorded for every intubation.

The mean of each trainee's 15 endoscopy times was paired with his or her AD2, AD3 and MAZE scores, and the correlation between endoscopy times and psychometric test scores were analysed using Pearson correlation coefficients and linear regression. The mean times for the first seven endoscopies and last seven endoscopies and the ratios of the mean times for the last seven endoscopies to the mean times for the first seven endoscopies were also studied. $P<0.05$ was considered statistically significant.

Results

Age, professional status and sex of the 16 trainees studied are given in table 1.

Table 1 Age, status and sex distribution of the trainees (mean [range] or number)

No of Trainees	Age (yr)	Professional status	Sex (M/F)
16	30.06 [26–36]	7 Specialist Registrars 9 Senior House Officers	12/4

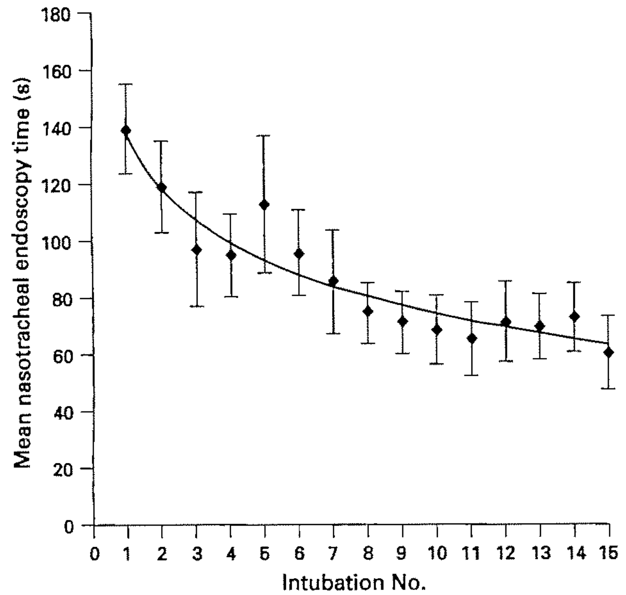

Figure 1 Mean (95% confidence intervals) fibreoptic nasotracheal endoscopy times for the 15 endoscopies performed by the 16 trainees.

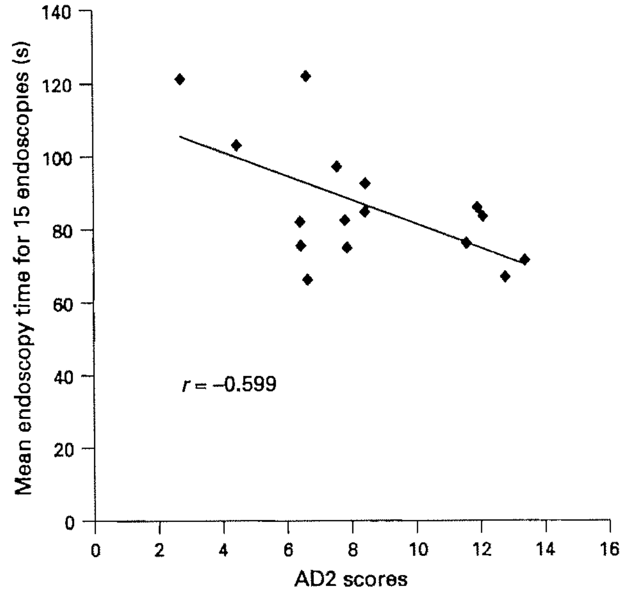

Figure 2 Association between the means of the first 15 fibreoptic nasotracheal endoscopy times and AD2 scores.

All trainees improved with fibreoptic intubation practice and mean endoscopy times decreased progressively during the first 15 endoscopies (fig.1).

There were significant correlations between mean endoscopy times for the 15 endoscopies and AD2 scores (table 2, fig. 2) and AD3 scores (table 2, fig. 3). Mean times for the first seven endoscopies (Nos 1–7) and for the last seven endoscopies (Nos 9–15) were also significantly correlated with AD2 and AD3 scores (table 2). Correlations between mean times for the 15 endoscopies, the first seven endoscopies and the last seven endoscopies and MAZE scores were not statistically significant (table 2, fig. 4).

The rates at which individual trainees improved varied considerably. The ratios of mean endoscopy times for the last seven endoscopies to mean endoscopy times for the first seven endoscopies varied from 0.46 to 0.79 (table 2). However, improvement ratios were not significantly correlated with AD2, AD3 or MAZE scores (table 2).

In order to minimize some of the effects resulting from trainees' encountering patients' airways of varying degrees of difficulty, the statistical analyses were repeated on the data when each trainee's fastest and slowest endoscopy times were omitted. Similar correlations to those above were found (table 3).

Discussion

We have shown that there was a significant negative correlation between mean times required by anaesthetic trainees to perform their first 15 fibreoptic endoscopies and scores on psychomotor tracking tests. This confirms the impression that manual dexterity, eye–hand co-ordination and other motor abilities are important determinants of an individual's initial level of endoscopy skill and performance.[8] However, there appeared to be no correlation between MAZE, an information processing test from the MICROPAT system, and endoscopy times. This suggests that the ability to process and use a sequence of fast-moving information, as tested by MAZE, is not a key aptitude when performing fibreoptic endoscopy. Further studies are required to determine the extent to which other information processing abilities are pertinent to fibreoscopy. MICROPAT embraces tests relevant to two of the three stages of Schmidt's closed-loop model for perceptual–motor skills,[1] but does not examine perception, the first stage. It is conceivable, however, that spatial orientation, complex visuospatial organization and other perceptual abilities are intimately involved in the skilful performance of

Table 2 Correlations coefficients (*r*) between AD2, AD3, MAZE and fibreoptic nasotracheal endoscopy time variables (for 15 endoscopies). *$P<0.05$

Endoscopy time variable	Mean of means	Range of means	Psychometric test	*r*
Mean endoscopy times for 15 endoscopies (s)	86.3	66–122	AD2	–0 599*
			AD3	–0 589*
			MAZE	–0 102
Mean endoscopy times for first 7 endoscopies (1–7) (s)	106.1	72–140	AD2	–0 523*
			AD3	–0 530*
			MAZE	–0 091
Mean endoscopy times for last 7 endoscopies (9–15) (s)	68.2	48–108	AD2	–0.558*
			AD3	–0.530*
			MAZE	–0 085
Ratios of mean endoscopy time for last 7 endoscopies (9–15) to mean endoscopy time for first 7 endoscopies (1–7)	0.64	0.46–0.79	AD2	–0 190
			AD3	–0.194
			MAZE	–0.002

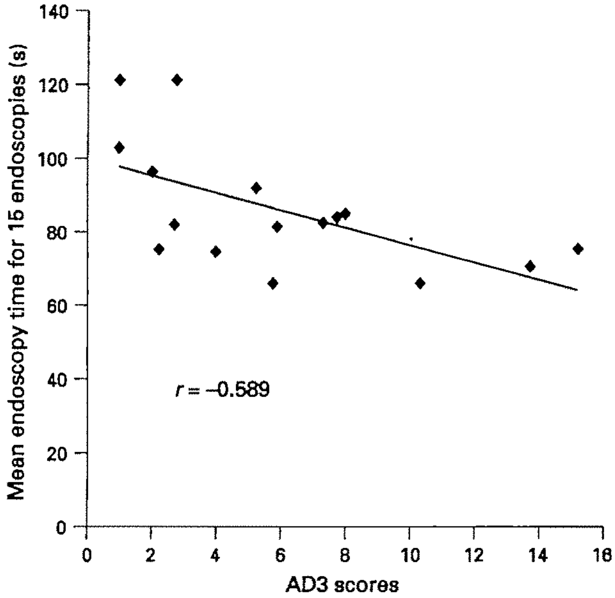

Figure 3 Association between the means of the first 15 fibreoptic nasotracheal endoscopy times and AD3 scores.

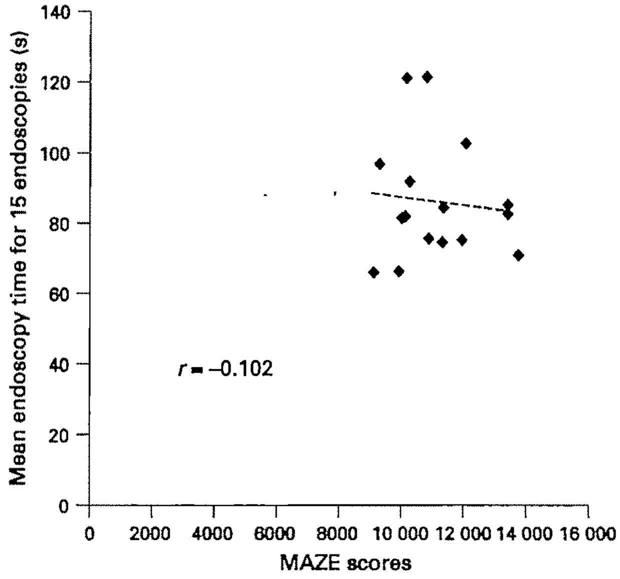

Figure 4 Association between the means of the first 15 fibreoptic nasotracheal endoscopy times and MAZE scores.

fibreoptic endoscopy. Perceptual processing has been shown to be necessary for laparoscopic manipulations[10] and Schueneman and colleagues have demonstrated that perceptual and information processing abilities were more accurate predictors of operative skill among surgical residents than psychomotor aptitude.[11 12] Academic achievements, incidentally, were found not to correlate, or even to correlate negatively, with surgical skill in Schueneman's studies,[11 12] as in others.[13] Sivarajan and colleagues studied anaesthetic residents as they learned spinal anaesthesia and also found that their academic knowledge of the technique did not correlate with their criterion-referenced clinical performance of it.[14]

It is important to note, however, that the rates at which trainees' times improved during their first 15 intubations were not significantly correlated with psychomotor scores. Hence, psychomotor abilities do not appear to be good predictors of the individual's rate of learning of fibreoptic skills during early training. One possible reason for this is that the study was designed to examine the initial stages of fibreoptic training, not the whole endoscopy learning process. There is evidence that the mean half-life for fibreoptic nasotracheal endoscopy learning is approximately nine endoscopies,[9] and this implies that the average trainee needs to perform at least 45 endoscopies before he approaches his asymptote or "expert time," when the learning process may be considered almost complete. Hence endoscopy records collected over a much longer period than in this study would be required to confirm or refute an association between psychomotor abilities and the rate of learning of fibreoscopy from novice to expert. When acquiring complex motor skills, beginners need first to go through the verbal–cognitive stage of learning.[1] Here, the main concern is to analyse what needs to be done, explore different strategies and elaborate the most effective and efficient technique for performing the task. Hence cognitive abilities may be more important during the early stages of motor learning, and psychomotor abilities may become more relevant in later stages, when cognitive problems have been solved.

MICROPAT psychomotor tracking tests were designed primarily as measures of eye–hand co-ordination and control precision for the selection of UK Army Air Corps pilots.[7] The initial validation study used a sample of 243 pilot trainees and found that the correlation coefficient between MICROPAT

Table 3 Correlations coefficients (r) between AD2, AD3, MAZE and fibreoptic nasotracheal endoscopy time variables for 13 endoscopies (each trainee's fastest and slowest times omitted). $^*P<0.05$

Endoscopy time variable	Mean of means	Range of means	Psychometric test	r
Mean endoscopy times for 13 endoscopies (s)	83.2	66–121	AD2	−0.577*
			AD3	−0.560*
			MAZE	−0.128
Mean endoscopy times for first 6 endoscopies (1–6) (s)	95.6	65–135	AD2	−0.499*
			AD3	−0.491*
			MAZE	−0.148
Mean endoscopy times for last 6 endoscopies (8–13) (s)	71.8	50–114	AD2	−0.551*
			AD3	−0.516*
			MAZE	−0.058
Ratios of mean endoscopy time for last 6 endoscopies (8–13) to mean endoscopy time for first 6 endoscopies (1–6)	0.75	0.53–0.97	AD2	−0.148
			AD3	−0.149
			MAZE	−0.129

tests and the criterion task of pilotry was 0.57 and thus MICROPAT measured approximately 33% $(r^2\times100)$[1,7] of the abilities underlying pilotry skills. The correlation coefficients between MICROPAT psychomotor tests and early endoscopy performance found in our study were remarkably similar. Thus psychomotor abilities may account for up to one-third of the variations in early endoscopy performance. It necessarily follows that psychomotor aptitude is by no means the only factor required for success in fibreoptic endoscopy, nor is it necessarily the most important factor. Cognitive and perceptual abilities are also likely to be crucially important. It is also essential to be well motivated, to have a positive mental attitude and to be able to focus one's attention. It is important to learn an effective endoscopy technique and to receive quality feedback guidance from an experienced instructor. Hence there is no reason why a low psychomotor test score should disqualify an anaesthetist from fibreoptic training; all trainees should have the opportunity to receive instruction in this technique.

Although none of the trainees in our study were computer games or arcade games devotees, most had access to personal computers and some recounted playing computer games on infrequent occasions while scholars or students. It is important to know if regular practice on such games significantly affects the scores obtained in psychometric tests. In general, it is believed that transfer between two similar skills tends to be small,[1] and Harvey[3] has stated that there are two reasons for this. First, skills that appear similar are often based on different combinations of abilities. Second, practice at a skill reduces the proportion of variance that can be explained by specific motor abilities and increases the proportion of variance that is specific to the skill itself. Hence there is proportionately less of a highly practised skill that is available for transfer. Instructors should thus be aware of the possibility that psychomotor scores achieved by computer games experts may, to a limited extent, reflect some transfer of learning, and this may also apply to trainees with other highly developed motor skills, for example experienced pilots or musical instrument players. There is no information on whether or not these skills are also correlated with fibreoptic endoscopy performance.

Although it is not essential for a trainee to undergo psychometric tests before embarking on a fibreoptic training programme, there may sometimes be advantages in having an objective evaluation of the individual's psychomotor aptitude. The information could be fed back to the trainee, in a constructive manner, as knowing one's strengths and weaknesses can provide an effective tool for optimizing progress and personal development. A particularly high psychomotor score might reinforce a recommendation for further endoscopy training. An awareness of an anaesthetist's psychomotor abilities may help instructors to tailor training programmes more effectively for the individual, for example by indicating which trainees may benefit from more extensive practice on airway simulators before embarking on treating patients.

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References

1. Schmidt RA. *Motor Learning and Performance: from Principles to Practice*. Champaign, Illinois. Human Kinetics Publishers, 1991
2. Fleishman EA A comparative study of aptitude patterns in unskilled and skilled psychomotor performances. *Journal of Applied Psychology* 1957; **41**: 263–272.
3. Harvey N. Skilled performance. In. Baum, eds. *Cambridge Handbook of Psychology, Health and Medicine*. Cambridge. Cambridge University Press, 1997; 50–55.
4. Bell JA. Royal Air Force selection procedures. *Annals of the Royal College of Surgeons of England* 1988; **70**: 270–275.
5. Holdsworth RF. Objective assessment—the state of the art. *Annals of the Royal College of Surgeons of England* 1988; **70**: 266–270.
6. Bartram D, Banerji N, Rothwell D, Smith P Task parameters affecting individual differences in pursuit and compensatory tracking performance. *Ergonomics* 1985; **28**: 1633–1652.
7. Bartam D. The development of an automated testing system for pilot selection: The MICROPAT project. *Applied Psychology: An International Review* 1987; **36**: 279–298.
8. Ovassapian A. *Fiberoptic Endoscopy and the Difficult Airway*, 2nd Edn. Philadelphia, Pennsylvania: Lippincott–Raven, 1996; 263–271.
9. Smith JE, Jackson APF, Hurdley J, Clifton PJM. Learning curves for fibreoptic nasotracheal intubation when using the endoscopic video camera. *Anaesthesia* 1997, **52**: 101–106.
10. Hanna GB, Drew T, Clinch P, Shimi S, Dunkley P, Hau C, Cuschieri A. Psychomotor skills for endoscopic manipulations: Differing abilities between right and left-handed individuals. *Annals of Surgery* 1997; **225**: 333–338
11. Schueneman AL, Pickleman J. Hesslein R, Freeark RJ. Neuropsychologic predictors of operative skill among general surgery residents. *Surgery* 1984; **96**: 288–295
12. Schueneman AL, Pickleman J, Freeark RJ. Age, gender, lateral dominance, and prediction of operative skill among general surgery residents *Surgery* 1985; **98**: 506–514
13. Lazar HL, DeLand EC, Tompkins RK. Clinical performance versus in-training examinations as measures of surgical competence. *Surgery* 1980; **87**: 357–362.
14. Sivarajan M, Miller E, Hardy C, Herr G, Liu P, Willenkin R, Cullen B. Objective evaluation of clinical performance and correlation with knowledge *Anesthesia and Analgesia* 1984, **63**: 603–797.

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Evaluation of routine tracheal extubation in children: inflating or suctioning technique?

J. Guglielminotti, I. Constant and I. Murat

Summary

We studied prospectively the effects of the technique of tracheal extubation on arterial haemoglobin oxygen saturation (Sp_{O_2}) in 120 ASA I–III children, mean age 5.3 (range 0.25–16.9) yr. At completion of surgery, tracheal extubation was performed when spontaneous ventilation had resumed, children were fully awake and Sp_{O_2} was 99–100%. Children were allocated randomly to receive a single lung inflation manoeuvre with 100% oxygen before tracheal extubation (group I; n=59) or to have the tracheal tube removed while applying suction through the tube (group S; n=61). Sp_{O_2} was monitored during the first 5 min after tracheal extubation in the operating room. Supplementary oxygen was given if Sp_{O_2} decreased to less than 92%. The time between tracheal extubation and decrease in Sp_{O_2} to 92% (T92) was recorded. Children in group S required oxygen administration more frequently after tracheal extubation than those in group I (65.6% *vs* 45.8%; P=0.04), and had a three-fold shortening of T92 (mean 25 (SD 19) s *vs* 85 (63) s; P=0.0001). These effects were more pronounced in children less than 4 yr of age compared with older children. We conclude that tracheal extubation greatly impaired oxygenation and therefore administration of oxygen was appropriate. This impairment was more marked when suction was used, and in young children. Lung inflation with 100% oxygen before removal of the tracheal tube is advised before routine tracheal extubation in children. (*Br. J. Anaesth.* 1998; **81**: 692–695).

Keywords: intubation tracheal, extubation; anaesthesia, paediatric; hypoxaemia; lung, volume

Hypoxaemia is the most frequently encountered respiratory complication during emergence from anaesthesia in children. Approximately 40% of children less than 4 yr old experience arterial haemoglobin oxygen desaturation to less than 90% within the first 15 min after tracheal extubation,[1] and approximately 30% on arrival in the post-anaesthesia care unit (PACU).[2] Tracheal extubation techniques may influence the incidence of arterial haemoglobin oxygen desaturation during this period. Indeed, removal of the tracheal tube while children are still deeply anaesthetized reduces desaturation episodes compared with awake tracheal extubation.[1] However, few studies have addressed the question of the influence of the tracheal tube removal technique itself.

Mehta reported that a technique combining pharyngeal suctioning followed by insertion of a suction catheter into the tracheal tube and removal of it while applying a negative pressure through the suction catheter eliminated pulmonary aspiration of a radiographic dye placed on the back of the tongue.[3] However, this technique may reduce lung volumes and oxygen stores, favouring arterial haemoglobin oxygen desaturation. These effects may be more pronounced in young children because of their reduced functional residual capacity (FRC) and high oxygen consumption.[4 5] As an alternative to a tracheal suctioning technique, a lung inflation manoeuvre with 100% oxygen before cuff deflation and removal of the tracheal tube has been advocated.[6] This technique would theoretically maintain the patient with a clear airway (by expelling retained secretions by the positive pressure gradient created between the lungs and atmosphere) and the lungs would be filled with oxygen. This inflation manoeuvre is now recommended in some anaesthesia textbooks[7] for routine tracheal extubation but it has never received clinical evaluation in daily anaesthesia practice. In particular, its effects on arterial haemoglobin oxygen saturation after removal of the tracheal tube are unknown.

Therefore, in this randomized, prospective, single-blind study, we assessed the effects of both extubation techniques (i.e. suctioning or inflating technique) on the frequency and onset of arterial haemoglobin oxygen desaturation after general anaesthesia in children, and the effects of age on the incidence of desaturation after tracheal extubation.

Patients and methods

After obtaining approval from our institute and informed consent from parents, we studied ASA I–III children undergoing elective surgery with general anaesthesia and orotracheal intubation. Patients with a full stomach, those undergoing thoracic surgical procedures, emergency surgery or ENT surgery, and those in whom intubation was rated difficult (defined as the need for more than two laryngoscopies) were excluded. No attempt was made to exclude children with upper respiratory tract infections if they were considered eligible for general anaesthesia by the attending anaesthetist.

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All children received oral or intrarectal premedication with midazolam 0.3–0.5 mg kg^{-1}. Administration of anaesthesia was left to the discretion of the attending anaesthetist. Anaesthesia was induced with propofol 3–5 mg kg^{-1} i.v. or inhaled sevoflurane according to the child's age and preference. Tracheal intubation with a cuffed tube was performed with sevoflurane alone or after i.v. administration of atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained with desflurane or isoflurane and 60% nitrous oxide in oxygen, supplemented with i.v. bolus doses of alfentanil or sufentanil. Ventilation was controlled mechanically. After completion of the surgical procedure, the inhaled anaesthetics and nitrous oxide were discontinued and the lungs ventilated with 100% oxygen. Tracheal and pharyngeal suctioning were performed while the children were still in the surgical plane of anaesthesia. After re-establishing spontaneous ventilation, neuromuscular block was antagonized with neostigmine 40 µg kg^{-1} and atropine 20 µg kg^{-1} if less than four responses were observed on TOF stimulation of the adductor pollicis muscle. The trachea was extubated when the child was responding to verbal command or was opening his (her) eyes, provided that Sp_{O_2} was 99–100%.

The choice of extubation technique was randomized on a daily basis. On odd days, the lungs received a single lung inflation manoeuvre with 100% oxygen before cuff deflation and removal of the tracheal tube (group I). On even days, a suction catheter was introduced into the tracheal tube until a resistance was met, the cuff was then deflated and the catheter was removed, together with the tracheal tube, while applying a negative pressure of −150 cm H_2O (group S). The suction catheter was chosen so that its external diameter was half the internal diameter of the tracheal tube. After tracheal extubation, children were observed for 5 min in the operating room while breathing room air. Forward jaw displacement was allowed for alleviating airway obstruction if necessary, and pharyngeal suctioning was performed if retained secretions were suspected. Oxygen was given by face mask if arterial haemoglobin oxygen saturation decreased to less than 92%. After 5 min, children were transferred to the PACU, provided that Sp_{O_2} was >97%.

Arterial haemoglobin oxygen saturation (Sp_{O_2}) was monitored using an age-appropriate probe placed on the toe with a N-200 or N-250 Nelcor pulse oximeter adjusted to rapid update mode (mean integration time 2–3 s; accuracy ±2% for 70–100%). Sp_{O_2} was recorded for 5 min in the operating room by an independent observer. This observer was not involved in the extubation procedure but was aware of the extubation technique used. The time between tracheal extubation and Sp_{O_2} to decrease to 92% (T92) was recorded, in addition to the occurrence of desaturation to less than 92%.

STATISTICAL ANALYSIS

Continuous data were compared using a two-sided *t* test and proportions with chi-square test. Kaplan–Meier analysis followed by the log-rank test was used to assess the effects of age on arterial haemoglobin oxygen desaturation after tracheal extubation. For this purpose, the population was divided into two groups: those more than 4 yr of age and those less than 4 yr. The end-point for Kaplan–Meier analysis was defined as the ability of a child to sustain an Sp_{O_2} equal to or greater than 92% (i.e. without supplementary oxygen administration) during the 5-min observation period in the operating room. $P<0.05$ was regarded as statistically significant. Data are expressed as mean (SD).

Results

We studied 120 children: 59 in the inflation group (I) and 61 in the suction group (S). Patient characteristics, anaesthetic technique and surgical procedures are presented in table 1.

The incidence of arterial haemoglobin oxygen desaturation requiring oxygen administration (i.e. less than 92%) in the operating room after tracheal extubation was significantly greater in group S compared with group I (table 2). Moreover, time to Sp_{O_2} to decrease to 92% after tracheal extubation was nearly three-fold shorter in group S compared with group I.

Kaplan–Meier survival curves are presented in figure 1. They demonstrate that, irrespective of the tracheal extubation technique used, the percentage of children with Sp_{O_2} ≥92% was greater in children aged more than 4 yr (*n*=60; 9.0 (3.9) yr) than in those aged less than 4 yr (*n*=60; 1.6 (1.0) yr) (fig. 1A). When the suctioning and inflating techniques are examined independently (fig. 1B, 1C), the percentage of children with Sp_{O_2} ≥92% was still greater in

Table 1 Patient characteristics, anaesthetic technique and surgical procedure (mean (SD or range) or number of children (%)). No significant differences between groups

	Inflation group	Suction group
Age (yr)	5 2 (0 29–16 7)	5.4 (0.25–16.9)
Weight (kg)	21.8 (17 5)	21.0 (13 6)
ASA status		
I	45 (76.2%)	53 (86.9%)
II or III	14 (23.8%)	8 (13 1%)
Duration of anaesthesia (min)	110 (56)	105 (58)
Opioid doses (µg kg^{-1})		
Alfentanil (*n*=41)	22.5 (7.7)	23.4 (14.3)
Sufentanil (*n*=58)	0.46 (0.27)	0.51 (0.38)
End-tidal concentration before tracheal extubation (%)		
Isoflurane (*n*=93)	0.19 (0 10)	0 20 (0.06)
Desflurane (*n*=20)	0.44 (0 22)	0 39 (0 24)
Neuromuscular blocking drugs		
None	41 (69.5 %)	47 (77 %)
Antagonism	1 (1.7 %)	0 (0%)
Surgical procedures		
Orthopaedic	17 (28 8%)	13 (21.3%)
Plastic	22 (37 3%)	25 (41 0%)
Abdominal and urological	13 (22.0%)	20 (32.8%)
Miscellaneous	7 (11.9%)	3 (4 9%)

Table 2 Number and percentage of children reaching an Sp_{O_2} of <92% in each group and time to onset of arterial haemoglobin oxygen desaturation after tracheal extubation during the 5-min observation period in the operating room (mean (SD) or number of children (%)). Oxygen was administered if Sp_{O_2} was less than 92% *$P<0.05$, ***$P<0.001$ *vs* inflation group

	Inflation group	Suction group
Sp_{O_2} <92%	27 (45.8%)	40 (65 6%)*
T92 (s)	85 (63)	25 (19)***

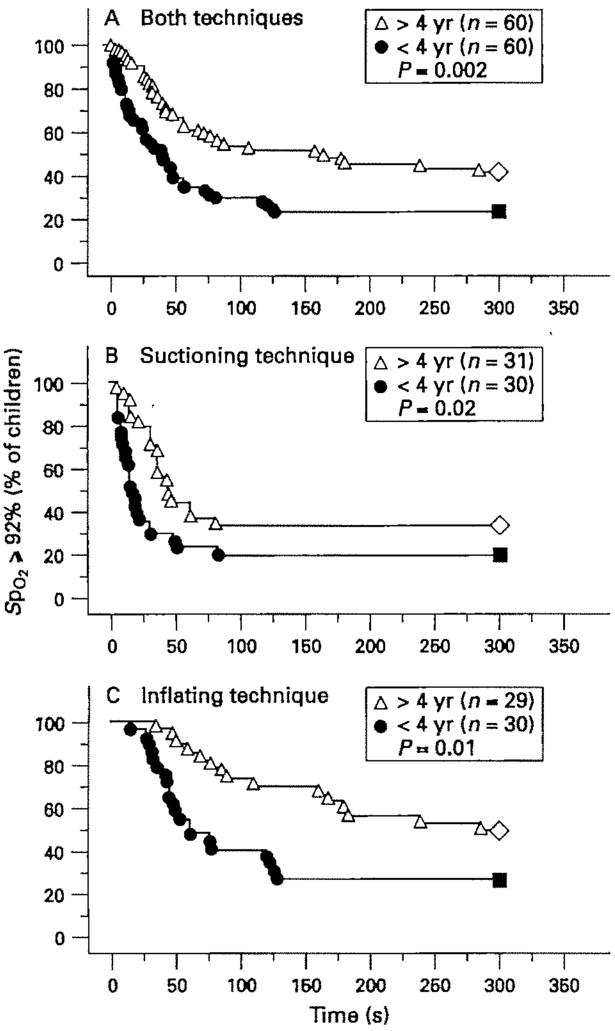

Figure 1 Effect of age on Kaplan–Meier survival curves for children undergoing tracheal extubation irrespective (A) or depending (B and C) on the technique used; the y axis represents the percentage of children who sustained Sp_{O_2} equal to or greater than 92% without oxygen administration during the 5-min observation period in the operating room.

children aged more than 4 yr compared with those aged less than 4 yr, irrespective of the technique used for tracheal extubation.

Discussion

In this prospective, randomized study, we demonstrated that a single lung inflation manoeuvre with 100% oxygen before removal of the tracheal tube reduced the need for supplementary oxygen therapy during the first 5 min after tracheal extubation, and delayed the onset of desaturation compared with a suctioning procedure. These effects were more pronounced in children less than 4 yr of age compared with older children.

The reduced incidence of desaturation episodes observed with the inflating technique indicates that lung volumes and lung oxygen stores are critical determinants of early desaturation after tracheal extubation in children, in agreement with clinical studies in adult apnoeic patients.[8] Indeed, there is an inverse relationship between both frequency and severity of desaturation after a 30-s voluntary apnoea in normal adult subjects, and pre-apnoea lung volume.[8] Similarly, maintaining lung volumes and oxygen stores with intratracheal oxygen lessens the frequency and severity of desaturation during apnoea in patients undergoing mechanical ventilation.[9 10] Conversely, tracheal suctioning reduces lung volumes, affecting shunt area appearance and hypoxaemia in critically ill patients undergoing mechanical ventilation.[10] However, these effects on oxygenation could not be extended to anaesthetized patients. They were assessed after disconnection from the ventilator, either when they were sedated or paralysed without spontaneous ventilation.[9–11] This differs markedly from the spontaneously breathing patient recovering from anaesthesia. In addition, a single lung inflation manoeuvre with 100% oxygen can suppress atelectasis and ventilation perfusion mismatches observed after experimental cardiopulmonary bypass, which are mainly responsible for postoperative hypoxaemia.[12]

Time to onset of hypoxaemia during apnoea is dependent on the balance between oxygen supply (i.e. alveolar oxygen tension and lung volume) and extraction from the circulating blood (i.e. oxygen consumption). In our study, time to desaturation to 92% was three-fold shorter when tracheal suctioning was applied compared with the inflation technique. This suggests that lung volumes and oxygen stores modulate the onset of desaturation after tracheal extubation in the spontaneously breathing child in the same way as in apnoeic patients.

There is a strong relationship between weight and FRC, and between weight and oxygen consumption in children.[4 5] This explains the positive relationship between age and onset of desaturation during apnoea: the younger the child, the more rapid the onset of desaturation.[13] Moreover, the difference between FRC and closing volume increases linearly with age up to 20 yr,[14] exposing younger children to a greater risk of postoperative hypoxaemia.[2] On this basis, we hypothesized that younger children might be more prone to desaturation after tracheal extubation, and that desaturation might occur more rapidly. To test this assumption, we used Kaplan–Meier survival curves and we defined survival as the ability of a child to maintain Sp_{O_2} ≥92% during the 5-min observation period in the operating room (i.e. without oxygen administration). This analysis takes into account both the onset and frequency of desaturation to less than 92%. Our data demonstrated that desaturation occurred earlier and was more frequent in children less than 4 yr of age, irrespective of the tracheal extubation technique used.

In summary, tracheal extubation greatly impairs oxygenation, and systematic oxygen administration after tracheal tube removal is of clinical value. This impairment is more pronounced with a suctioning technique and in young children. A lung inflation manoeuvre with 100% oxygen before removal of the tracheal tube may be advised for routine extubation in children.

References

1. Pounder DR, Blackstock D, Stewart DJ. Tracheal extubation in children: halothane versus isoflurane, anesthetized versus awake. *Anesthesiology* 1991; 74: 653–655.
2. Xue FS, Huang YG, Tong SY, Liu QH, Liao X, An G, Luo LK, Deng XM. A comparative study of early postoperative hypoxemia in infants, children, and adults undergoing elective plastic surgery. *Anesthesia and Analgesia* 1996; 83: 709–715.

3. Mehta S. The risk of aspiration in the presence of cuffed endotracheal tubes. *British Journal of Anaesthesia* 1972; **44**: 601–605
4. Lindahl SGE. Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery. *British Journal of Anaesthesia* 1989; **62**: 70–76.
5. Thorsteinsson A, Jonmarker C, Larsson A. Functional residual capacity in anesthetized children: normal values and values in children with cardiac anomalies. *Anesthesiology* 1990; **73**: 876–881.
6. Cheney D. The risk of aspiration in the presence of cuffed endotracheal tubes. *British Journal of Anaesthesia* 1972; **44**: 1335.
7. Stone DJ, Gal TJ. Airway management. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone, 1994; 1403–1435.
8. Findley LJ, Ries AL, Tisi GM, Wagner PD. Hypoxemia during apnea in normal subjects: mechanisms and impact of lung volume. *Journal of Applied Physiology* 1983; **55**: 1777–1783.
9. Boba A, Cincotti JJ, Piazza TE, Landmesser CM. The effects of apnea, endotracheal suction, and oxygen insufflation, alone and in combination, upon arterial oxygen saturation in anesthetized patients. *Journal of Laboratory and Clinical Medicine* 1959; **53**: 680–685.
10. Brochard L, Mion G, Isabey D, Bertrand C, Messadi AA, Mancebo J, Boussignac G, Vasile N, Lemaire F, Harf A. Constant-flow insufflation prevents arterial oxygen desaturation during endotracheal suctioning. *American Review of Respiratory Diseases* 1991; 144: 395–400.
11. Boutros AR. Arterial blood oxygenation during and after endotracheal suctioning in the apneic patient. *Anesthesiology* 1970; **32**: 111–118.
12. Magnusson L, Zemgulis V, Tenling A, Wernlund J, Tyden H, Thelin S, Hedenstierna G. Use of a vital capacity maneuver to prevent atelectasis after cardiopulmonary bypass: an experimental study. *Anesthesiology* 1998; **88**: 134–142.
13. Kinouchi K, Tanigami H, Tashiro, Nishimura M, Fukumitsu K, Takachi Y. Duration of apnea in anesthetized infants and children required for desaturation of hemoglobin to 95%. *Anesthesiology* 1992, **77**: 1105–1107.
14. Mansell A, Bryan C, Levison H. Airway closure in children *Journal of Applied Physiology* 1972; **33**: 711–714.

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Non-invasive aortic blood flow measurement in infants during repair of craniosynostosis†

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Summary

We have assessed the potential clinical benefit of a new echo-Doppler device (Dynemo 3000) which provides a continuous measure of aortic blood flow (ABF) using an aortic flowmeter and a paediatric oesophageal probe, during repair of craniosynostosis in infants under general anaesthesia. The data recorded included: ABFi (i=indexed to body surface area), stroke volume (SVi), systemic vascular resistance (TSVRi), pre-ejection period (PEP), left ventricular ejection time (LVET), mean arterial pressure (MAP), heart rate (HR) and central venous pressure (CVP). Data were collected: before (T1) and 3 min after skin incision (T2), at the time of maximal haemorrhage (T3) and at the end of the procedure (T4). Twelve infants (aged 7.0 (range 6–12) months) were included. ABFi, MAP and CVP were significantly lower at T3 compared with T1 (2.0 (0.8) *vs* 3.0 (0.8) litre min^{-1} m^{-2}, 46.1 (5.8) *vs* 65.2 (8.9) mm Hg and 2.8 (1.6) *vs* 5.2 (2.1) mm Hg; $P<0.05$). PEP/LVET ratio was significantly lower at T2 compared with T1 (0.25 (0.05) *vs* 0.30 (0.06)) and increased at T4 (0.36 (0.04); $P<0.05$). These preliminary results suggest that this non-invasive ABF echo-Doppler device may be useful for continuous haemodynamic monitoring during a surgical procedure associated with haemorrhage in infants. (*Br. J. Anaesth.* 1998; **81**: 696–701).

Keywords: complications, craniosynostosis; blood, flow; measurement techniques, ultrasound; anaesthesia, paediatric

Craniosynostosis is a relatively common disorder, with an estimated incidence of 1 per 2000 live births, related to premature closure of skull sutures.[1,2] An early surgical correction is mandatory in the majority of cases because the compensatory deformation of the skull which occurs during rapid growth of the brain in early infancy may lead to increased intracranial pressure, especially in children older than 1 yr of age, and particularly if multiples sutures are involved.[3] Surgery is aimed at restoring normal anatomy at an early age to achieve the best cosmetic result and avoid possible cerebral consequences.[2,4] Therefore, surgical procedures for correction of craniosynostosis are performed in young infants with a small blood volume and represent major surgery with extensive blood loss.[5,6]

Accurate determination and precise restoration of blood losses represent the major concern for the anaesthetist during this surgery. However, intraoperative assessment of blood loss is difficult and requires precise haemodynamic monitoring. Although it has been argued that invasive measurement of cardiac output allows earlier interventions during critical surgical procedures, the technical difficulties of inserting balloon catheters into small children are such that haemodynamic evaluation frequently relies solely on clinical monitoring (heart rate, arterial pressure, pulse oximetry and $P\text{E}'_{CO_2}$). Unfortunately, clinical assessment of cardiac function using these measurements has been shown to be unreliable in children.[7]

Experience with intraoperative transoesophageal echocardiography is limited in children,[8] and this monitoring is not widely available for infants. Moreover, the data provided by cardiac echocardiography only allow a diagnosis of a cardiovascular status at a given moment during the peroperative period.

These factors encouraged the development of non-invasive ultrasound techniques to measure cardiac output in newborns and infants. The oesophageal route was first used in an attempt to overcome the problems noted with the suprasternal route[9] and was progressively developed and improved by INSERM (U281) in France.[10,11] Application of this methodology in adults during general anaesthesia and in intensive care patients revealed the clinical usefulness of aortic blood measurement.[12–16] Non-invasive haemodynamic monitoring can now be performed with an echo-Doppler aortic blood flowmeter (Dynemo 3000 Sometec Inc., France). A miniaturized probe has been developed to continuously measure descending thoracic aortic diameter and blood velocity simultaneously, in infants as in adults. The aim of our preliminary study was to assess the feasibility and likely clinical benefits of continuous measurement of aortic blood flow (ABF) during repair of craniosynostosis, a surgical procedure associated with significant haemorrhage.

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Patients and methods

After obtaining approval from the Ethics Committee and informed consent from parents, we studied prospectively 12 infants (aged 6 months to 1 yr), ASA I–II, with a body weight of 6–12 kg, undergoing surgical repair of craniosynostosis. Exclusion criteria were: known or suspected oropharyngeal, oesophageal, aortic or mediastinal pathology; severe gastro-oesophageal reflux; or known or suspected latex sensitization.

All procedures were performed under general anaesthesia without induced hypotension after skull skin infiltration with epinephrine (adrenaline) 1:200 000 in normal saline. After premedication with clorazepate dipotassium, general anaesthesia was induced with 2–3% halothane followed by fentanyl 5 μg kg^{-1}. Neuromuscular block was achieved with atracurium 0.5 mg kg^{-1}. After orotracheal intubation, general anaesthesia was maintained using continuous i.v. infusion of fentanyl and controlled ventilation with 0.8–1.5% isoflurane and 50% nitrous oxide in oxygen. Monitoring included continuous ECG, invasive arterial and central venous pressures, core temperature, pulse oximetry, end-tidal carbon dioxide concentration and urine output.

Preoperative blood samples were obtained for measurement of red blood cells, platelet count, haemoglobin concentration, packed cell volume (PCV) and coagulation screen. Serial blood samples were obtained at least every 2 h during operation and as frequently as clinically indicated, for measurement of blood-gas tensions and PCV. Intraoperative management was as described previously.[5] Briefly, an isovolaemic compensation of blood loss was strictly observed, with fluid replacement based on haemodynamic variables, and including human serum albumin, colloids and packed red blood cells in order to maintain PCV in the range 0.28–0.35. Fresh frozen plasma was used only in patients requiring more than 70% of estimated blood volume transfusion.

MEASUREMENT PRINCIPLE

Velocity is measured using the Doppler formula: $v=((Cx\Delta F)/(2Fey(x)\cos I))$ where C=ultrasound velocity inside the blood, ΔF=frequency variation of emitted ultrasound, Fe=emission frequency, and I=angle of incidence and reflection of ultrasound against the red cells. Determination of ABF requires simultaneous and continuous measurement of the aortic section and blood velocity inside the aorta, at the same anatomical level where the aorta and oesophagus are nearly parallel. Using the specially designed ultrasound paediatric probe introduced into the oesophagus, we measured the diameter of the descending thoracic aorta using an M-mode echographic system and blood flow velocity with a pulsed Doppler velocimeter.

PROBE AND FLOWMETER

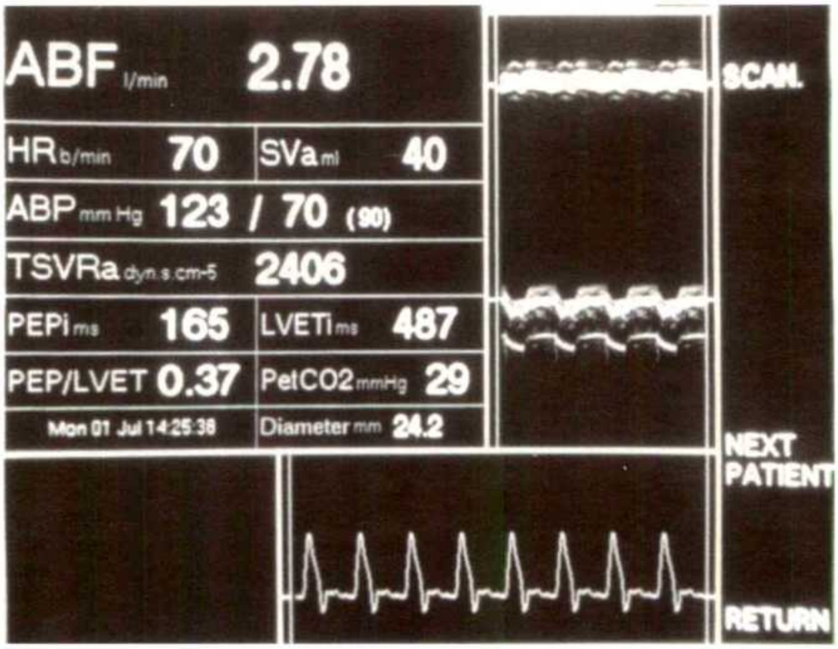
The paediatric oesophageal probe has two ultrasound transducers (3x3 mm) located at the distal part of the probe. The first operates at 10 MHz M-echo mode scanner, perpendicular to the centre line. The second is a Doppler pulsed emission transducer operating at 5 MHz and mounted at an angle of 60° to the centre line of the probe: the pulsed Doppler is emitted with a 48° divergent beam and the gated Doppler signal depth is adapted automatically to the aortic wall location values. This small probe, specially designed for newborns and infants, measures 5 mm (external diameter) and is 45 cm long. For infants, an 8- or 12-mm diameter cylindrical latex balloon is mounted on the sheath ready to be filled with 0.5 or 2 ml of water. This inflated balloon which surrounds the transducer maintains a constant angle of incidence of the ultrasound beams and allows the captor to rotate freely inside it without contact against the oesophageal mucosal wall. The balloon ensures transmission of ultrasound waves without air interposition and dissipates any heat produced.

The oesophageal probe was inserted and positioned immediately after induction of anaesthesia. Depth of introduction of the probe into the oesophagus varied according to the height of the infant and was measured between the echo transducer placed on the third intercostal juxtasternal space and a slide rubber ring placed at the level of the mouth. This distance approximated the level where the aorta and oesophagus are parallel.

The flowmeter includes three main parts: M-mode imaging system for diameter measurement, pulsed Doppler for velocity measurement, a second microprocessor system controlling flowmeter functions and peripheral monitoring devices. An invasive arterial cannula provides continuous measurement of mean arterial pressure (MAP). An electrocardioscope collects the ECG signal and calculates heart rate (HR) (Merlin, Hewlett Packard, USA). The haemodynamic profile integrates ABF, MAP and HR to calculate stroke volume (SV) in the descending aorta (obtained from the formula: SVa (ml)=ABF/HR) and total systemic vascular resistance (TSVR) (calculated from the formula: TSVRa (dyn s cm^{-5})=MAP/ABFx79.9). These two variables are indexed to ABF. Moreover, systolic time intervals (STI) are measured from computerized analysis of the ECG signal (Q wave detection) and the acceleration signal which is derived from the Doppler velocity signal. Opening and closing of the aortic valve are detected by computerized analysis of the acceleration signal. The computer determines the length of the pre-ejection period (PEP) between the Q wave and the beginning of the systolic acceleration front, corresponding to aortic valve opening. Starting at the end of PEP, measurement of the left ventricular ejection time (LVET) is obtained by searching the acceleration signal for the second maximum of systolic deceleration corresponding to aortic valve closure.[17] PEPi and LVETi are measured automatically and continuously and indexed to HR according to the formula of Weissler, Harris and Schoefeld.[18] PEP/LVET ratio is also calculated automatically. These values are presented in table form and updated every 8 s on a screen display (fig. 1). Finally, the haemodynamic profile is recorded every 8 s (or at the operator's request) on soft magnetic support.

MEASUREMENT FOR THE STUDY

When the recorded ABF was satisfactory (stable and clear images of aortic walls and Doppler velocity signal on the screen for more than 1 min), initial data, before skull skin infiltration and skin incision, were



ABF l/min 2.78

HR b/min 70 SVa ml 40

ABP mm Hg 123 / 70 (90)

TSVRa dyn.s.cm-5 2406

PEPi ms 165 LVETi ms 487

PEP/LVET 0.37 PetCO2 mmHg 29

Mon 01 Jul 14:25:38 Diameter mm 24.2

Figure 1 The Dynemo 3000 device. On the upper part of the screen, the M-mode echo of the aortic walls; on the lower part, the Doppler flow velocity. On the left part of the screen, the haemodynamic data shown in table form (updated every 8 s).

collected simultaneously and served as control values (T1). A second, third and fourth set of haemodynamic measurements were collected using the same criteria, respectively, 3 min after skin incision (T2), 60 min after skin incision (T3) and at the end of the surgical procedure during skin closure (T4). The time T3 was chosen at 60 min after skin incision because preliminary results had shown that at this time blood loss was maximal, with important haemodynamic changes. The oesophageal probe was removed at the end of surgery before discontinuation of anaesthesia.

In an attempt to simplify estimation of blood loss, red cell volumes were used. Estimated body volume (EBV)=80 ml kg^{-1} and red cell volume (ERCV)=EBVxPCV were calculated before operation. The following variables were then calculated for the period during operation: estimated red cell volume transfused (RCT)=0.75xvolume of packed red cells; estimated red cell volume deficit (ERCD)=ERCVxPCV variation; estimated red cell volume lost (ERCL)=ERCD+RCT; and percent of ERCV lost=ERCL/ERCV.

Results are reported as mean (SD). Data were compared between T1, T2, T3 and T4 using repeated measures analysis of variance and the Newman–Keuls test.[19] All *P* values were two-tailed, and $P<0.05$ was required to reject the null hypothesis. Statistical analysis was performed using NCSS 6.0 software (BMDP Company, Los Angeles, CA, USA).

Results

We studied 12 infants (eight females), treated by the same surgeon; mean age, weight, height and body surface area were 7.0 (range 6–12) months, 7.9 (SD 1.4) kg, 66.7 (3.9) cm and 0.39 (0.06) m^2, respectively. The nature of the skull deformity was: plagiocephaly in four patients, trigonocephaly in four, scaphocephaly in three and brachycephaly in one. Mean duration of anaesthesia was 236 (37) min, while mean duration of the surgical procedure was 140 (26) min. Total estimated red blood cells lost during the intraoperative period was 158 (77) % of preoperative estimated red cell volume (range 75–213%). ERCV, RCT, ERCD, ERCL and percent of ERCV lost are presented in table 1.

Mean intraoperative transfusion was 360.0 (169.7) ml (range 180–480 ml) of packed red blood cells.

No untoward incidents were noted using the device. Aortic diameter and ABF measurements were easily obtained in all cases and recording quality was excellent in all patients. However, it was necessary to reposition the oesophageal probe a mean of three times per patient because of loss of the Doppler signal related to displacement of the probe. These displacements were secondary to necessary movements of the head of the infant during the surgical procedure. Table 2 shows the haemodynamic variations during the surgical procedure: ABF, SVa and TSVRa were indexed to body surface area (ABFi, SVi, TSVRi). MAP, CVP and ABFi showed parallel changes in individual patients during the procedure (fig. 2).

There was no significant variation in HR, SVi or TSVRi during operation. ABFi, MAP and CVP decreased significantly ($P=0.0475$, $P<0.001$, $P=0.047$, respectively) at the time of maximal blood loss (T3) compared with T1. While CVP and ABFi were not significantly different from control values (T1) at the end of the procedure (T4), MAP remained significantly decreased ($P<0.01$). PEPi and PEP/LVET ratio was significantly decreased at the time of skin incision ($P<0.01$, $P<0.01$, respectively) and increased at the end of the procedure ($P<0.01$,

Table 1 Mean (SD) blood loss during the study

Estimated red cell volume lost (ml)	281 (119)
Packed red cell volume transfused (ml)	270 (127)
% of patient's estimated red cell volume lost (%)	158 (77)
Final red cell volume deficit (ml)	11 (8)

Table 2 Haemodynamic variations induced by skin incision (T2), blood loss (T3) and at the end of procedure (T4) compared with control values (T1). Data are mean (SD) (95% confidence interval). HR=Heart rate, MAP=mean arterial pressure, ABFi=aortic blood flow (indexed to body surface area), PEPi=pre-ejection period, LVETi=left ventricular ejection time, SVi=stroke volume (indexed to body surface area), TSVRi=total systemic vascular resistance (indexed to body surface area), CVP=central venous pressure. *$P<0.05$ *vs* T1

Measurement	T1	T2	T3	T4
HR (beat min^{-1})	110 (12) (102–117)	117 (16) (107–127)	110 (16) (101–120)	109 (9) (102–115)
MAP (mm Hg)	65 (9) (60–71)	69 (13) (60–77)	46 (6) (42–49)*	54 (4) (51–57)*
ABFi (litre min^{-1} m^{-2})	3.0 (0.8) (2.5–3.5)	3.8 (1.5) (2.7–4.8)	2.0 (0.8) (1.5–2.5)*	3 1 (1.6) (2.0–4.2)
PEPi (ms)	131 (20) (118–144)	112 (17) (99–123)*	136 (8) (130–141)	148 (10) (142–155)*
LVETi (ms)	467 (23) (453–482)	468 (21) (454–482)	462 (29) (443–480)	437 (21) (423–451)*
PEP/LVET	0.30 (0.06) (0.26–0.34)	0.25 (0.05*) (0.21–0.28)	0.31 (0.04) (0.29–0.34)	0.36 (0.04) (0.33–0.39)*
SVi (ml m^{-2})	29 (8) (24–33)	33 (13) (25–42)	25 (19) (13–38)	31 (15) (21–42)
TSVRi (dyn s cm^{-5} m^{-2})	2003 (822) (1481–2526)	1998 (1315) (1114–2882)	2269 (1454) (1345–3193)	2352 (1533) (1322–3382)
CVP (mm Hg)	5 (2) (4–7)	5 (2) (4–7)	3 (2*) (2–4)	6 (3) (4–7)

$P<0.01$, respectively). LVETi was significantly decreased at the end of operation ($P=0.015$).

Discussion

The main result of this preliminary clinical study was that non-invasive aortic blood measurement was feasible during repair of craniosynostosis in children, and estimated complementary haemodynamic trends. The echographic image of the aortic walls and Doppler flow were recorded easily without delay. The haemodynamic data appeared reliable in all cases and similar trends for each infant during surgical repair of craniosynostosis and haemorrhage were obtained: ABFi, MAP and CVP were decreased at the time of maximal blood loss (T3).

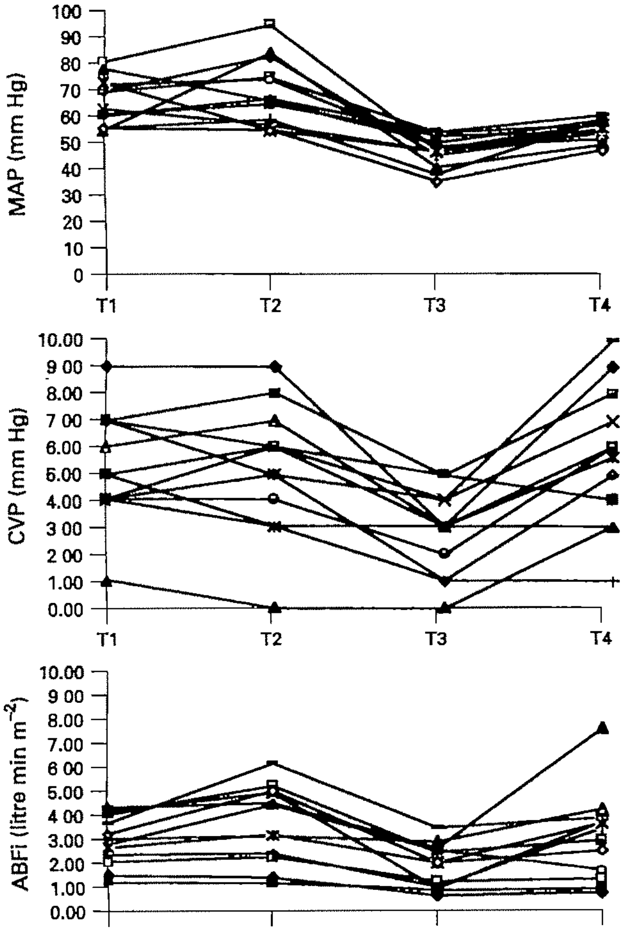


Figure 2 Evolution of MAP, CVP and ABFi in individual patients. MAP, CVP and ABFi showed parallel changes in individual patients. The same symbols are used for the same patients in the three figures.

The variations in systolic time intervals are a reflection of the inotropic variables: PEP reflects the isometric phase and LVET the isotonic phase of left ventricular contraction. A simplified expression of alterations in systolic time intervals is provided by the ratio PEP/LVET: among normal subjects this ratio averages 0.35±0.04. In adults, increase in PEP/LVET to 0.44 denotes decreased left ventricular performance.[20] In contrast, decreases in PEP and PEP/LVET are observed with the use of inotropic drugs. Therefore, the decreases in PEPi and PEP/LVET ratio noted on T2, combined with a non-significant increase in both MAP and ABFi may be related to the positive inotropic effect of epinephrine, used for skull skin infiltration. The increase in PEP/LVET ratio, observed at the end of the surgical procedure, indicated some decrease in left ventricular contractility,[21] which was not clinically relevant because ABFi was comparable with control values. This impairment in systolic time interval ratio could be related to metabolic acidosis and hypocalcaemia secondary to the massive blood transfusion. It was of interest to note that despite a significant decrease in MAP, ABFi and CVP at T3, there was no significant increase in TSVRi. This result could be related to the fact that general anaesthesia blunts the circulatory response to haemorrhage.[22]

Although it has been argued that invasive measurement of cardiac output allows earlier interventions in seriously ill patients or during critical surgical procedures, the practical problems of inserting a pulmonary artery catheter into small children are such that this monitoring device is not used routinely. Thus there is a need in paediatric critical care, and during critical paediatric anaesthesia, for an easy, accurate non-invasive measurement of blood flow.

Blood flow measurement using ultrasound techniques represents a suitable approach during general anaesthesia[23] and has acceptable agreement and precision compared with the direct Fick method. In fact, this non-invasive method has been shown previously to correlate well with electromagnetic flow in animals[24,25] and with thermodilution in humans.[12–14] The device allows measurement of aortic diameter and velocity at the same anatomical level continuously and non-invasively. The importance of this simultaneous measurement has been outlined previously in adults[26] and in children.[27] Moreover, aortic diameter is probably the most important single determinant of Doppler cardiac output.[28,29] Errors in measurement of aortic diameter are magnified because the square of the diameter is integrated into the calculated cardiac output.[30] It is well established that aortic diameter changes during the cardiac cycle[31,32] and with pressure, the relationship being almost linear.[31–34] For the purpose of our study we used a device which is the only one available enabling simultaneous measurement of aortic diameter and velocity. Until recently, this monitoring technique was not available in infants, however the recent development of a miniaturized probe has remedied this. Gueugniaud and colleagues have demonstrated the feasibility of this device in infants and have shown some myocardial depression from isoflurane.[35] However, contrary to our study, MAP was not measured continuously, which may have influenced the results, especially regarding the calculation ofTSVRa (MAP/ABFx79.9).

In summary, our results have confirmed the feasibility of this device and that it may provide non-invasive, complementary haemodynamic trends during a haemorrhagic surgical procedure in infants. Further studies are needed to evaluate how this new monitoring device may influence the perioperative management of infants and children.

Acknowledgements

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References

1. Marchac D, Renier D. Classification of the different types of craniosynostosis. In Marchac D, Renier D, eds. *Craniofacial Surgery for Craniosynostosis*. Boston: Little Brown, 1982; 1–8.
2 Lajeunie E, Lemerrer M, Bonaïti-Pellie C, Marchac D, Renier D. A genetic study of non syndromic coronal craniosynostosis. *American Journal of Medical Genetics* 1995; 55: 500–504
3. Renier D. Intracranial pressure in craniosynostosis: pre and postoperative recordings, correlation with functional results. In: Edgerton MT, Jane SA, eds. *Scientific Foundation and Surgical Treatement of Craniosynostosis* Baltimore: Williams and Wilkins, 1989; 263–269.
4. Meyer P, Renier D, Blanot S, Orliaguet G, Arnaud E, Lajeunie E. Anesthésie-Réanimation des craniosténoses et dysmorphies craniofaciales de l'enfant. *Annales Françaises d'Anesthésie et de Réanimation* 1997; **16**: 152–164.
5. Kearney RA, Rosales JK, Howes WJ. Craniosynostosis: an assessment of blood loss and transfusion practices. *Canadian Journal of Anaesthesia* 1989; **36**: 473–477.
6. Meyer P, Renier D, Arnaud E, Jarreau MM, Charron B, Buy E, Buisson C, Barrier G. Blood loss during repair of craniosynostosis. *British Journal of Anaesthesia* 1993; **71**: 854–857.
7. WolfWJ, Neal MB, Peterson MD. The hemodynamic and cardiovascular effects of isoflurane and halothane anesthesia in children. *Anesthesiology* 1986; 64. 328–333.
8. Reich DL, Konstadt SN, Nejat M, Abrams HP, Bucek J. Intraoperative transesophageal echocardiography for the detection of cardiac preload changes induced by transfusion and phlebotomy in pediatric patients. *Anesthesiology* 1993; **79**: 10–15.
9. Daigle RE, Miller CW, Histand MB, McLeod FD, Hokanson DE. Nontraumatic aortic blood flow sensing by use of an ultrasonic esophageal probe. *Journal of Applied Physiology* 1975; **38**: 1153–1160.
10. Cathignol D, Fourcade C. Sonde intracorporelle ultrasonore. Brevet INSERM no 78–14494
11. Lavandier B, Cathignol D, Muchada R, Bui Xuan B, Motin J. Noninvasive aortic blood flow measurement using an intraesopheageal probe. *Ultrasound in Medicine and Biology* 1985; **11**: 451–460.
12. Muchada R, Lavandier B, Cathignol D, Lamazou J, Lucchesi G, Roux MJ, Haro D, Palayer C. Non invasive haemodynamic monitoring in gynaecological laparoscopy. *Annales Françaises d'Anesthésie et de Réanimation* 1986; **5**: 14–17.
13. Muchada R, Cathignol D, Lavandier B, Lamazou J, Haro D. Aortic blood flow measurement. *American Journal of Noninvasive Cardiology* 1988; **2**: 24–31.
14. Muchada R, Cathignol D. Esophageal measurement of aortic blood flow by echo-Doppler. In: Vincent JL, ed. *Update in Intensive Care and Emergency Medicine*. Berlin. Springer Verlag, 1987; 356–365.
15. Gueugniaud PY, Caritat R, Barreiro G, Muchada R, Bertin-Maghit M, Petit P. Noninvasive haemodynamic monitoring for burnt patients: feasibility and usefulness of aortic blood flow measurement. *Réanimation Urgences* 1993; **2**. 533–538.
16 Gueugniaud PY, Muchada R, Bertin-Maghit M, Griffith N, Petit P. Non invasive continuous haemodynamic and PetCO2 monitoring during peroperative cardiac arrest. *Canadian Journal of Anaesthesia* 1995; **42**: 910–913.
17. Muchada R, Vernier F, Fady JF, Haro D, Lavandier B, Cathignol D. A new automatic measurement method of systolic time intervals (STI). *Journal of Cardiothoracic and Vascular Anesthesia* 1992; **6** (Suppl.1): 22.
18. Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation* 1968; **37**: 149–156
19. Fisher DM. Statistics in anesthesia In: Miller RD, ed. *Anesthesia* 2nd Edn. New York: Churchill Livingstone, 1986; 685–712.
20. Weissler AM Current concepts in cardiology. Systolic time intervals. *New England Journal of Medicine* 1977; **296**: 321–324.
21. Boudoulas H. Systolic time intervals. *European Heart Journal* 1990; **11** (Suppl.1): 93–104.
22. Vatner SF. Effects of anesthesia on cardiovascular control mechanisms. *Environmental Health Perspectives* 1978, **26**: 193–206.
23. Mark JB, Steinbrook RA, Gugino LD, Maddi R, Hartwell B, Shemin R, DiSesa V, Rida WN. Continuous noninvasive monitoring of cardiac output with esophageal Doppler ultrasound during cardiac surgery. *Anesthesia and Analgesia* 1986, **65**: 1013–1020.
24. Lavandier B, Muchada R, Chignier E, Fady JF, Birer A, Cathignol D. Assessment of a potentially noninvasive method for monitoring aortic blood flow in children. *Ultrasound in Medicine and Biology* 1991; **17**: 107–116.
25. Muchada R, Rinaldi A, Cathignol D. Non-invasive cardiovascular monitoring during general anaesthesia. *Minerva Anestesiologica* 1990; **56**: 199–205.
26. Muchada R, Cathignol D, Fontaine B, Lavandier B. Will morphometric data permit the determination of thoracic aorta caliber for precise measurement of blood flow in adults. *Journal d'Echographie et de Médecine pars Ultrason* 1990; **11**: 76–80.
27. Muchada R, Rinaldi A, Lavandier B, Cathignol D Transesophageal Doppler ultrasound in children: importance of aortic diameter evaluation audits change for the evaluation of aortic output. *Minerva Anestesiologica* 1992; **58**: 347–353.
28 Lucas CL, Keagy BA, Hsia HS, Johnson TA, Henry GW, Wilcox BR. The velocity profile in the canine ascending aorta and its effects on the accuracy of pulsed Doppler determinations of mean blood velocity. *Cardiovascular Research* 1984; **18**: 282–293.
29. Mehta N, Iyawe VI, Cummin ARC, Bayley S, Saunders KB, Bennet D. Validation of a Doppler technique for beat-to-beat measurement of cardiac output. *Clinical Science* 1985; **69**: 337–382.
30. Nishimura RA, Callahan MJ, Schaff HV, Ilstrup DM, Miller FA, Tajik AJ. Noninvasive measurement of cardiac output by continuous-wave Doppler echocardiography: Initial experience and review of the literature. *Mayo Clinic Proceedings* 1984; **59**: 484–489

31. Greenfield JC, Patel DJ. Relationship between pressure and diameter in the ascending aorta of man. *Circulation Research* 1962; **10**: 778–781.
32. Rushmer RF. Pressure-circumference relations in the aorta. *American Journal of Physiology* 1955; **33**: 545–549.
33. Barnett GO, Mallos AJ, Shapiro A. Relationship of aortic pressure and diameter in the dog. *Journal of Applied Physiology* 1961; **16**: 545–548.
34. Patel DJ, deFreitas FM, Greenfield JC, Fry DL. Relationship of pressure along the aorta in living dogs. *Journal of Applied Physiology* 1963; **18**: 1111–1117.
35. Gueugniaud PY, Muchada R, Moussa M, Haro D, Petit P. Continuous oesophageal aortic blood flow echo-Doppler measurement during general anaesthesia in infants. *Canadian Journal of Anaesthesia* 1997; **44**: 745–746.

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Haemodynamic stability and ketamine–alfentanil anaesthetic induction

R. I. Katz, A. Levy, B. Slepian, B. Sobel and R. S. Lagasse

Summary

We have determined if alfentanil could obtund the haemodynamic instability commonly seen at induction of anaesthesia with ketamine. Five groups of ASA I and II patients received ketamine 1 mg kg^{-1} i.v., preceded by saline (group 1) or alfentanil 10, 20, 30 or 40 μg kg^{-1} (groups 2–5, respectively). Heart rate (HR), mean arterial pressure (AP), postoperative patient complaints and dysphoria were noted. All groups showed increases ($P<0.05$) in both HR and AP after administration of ketamine, which were progressively smaller as the dose of alfentanil increased. After tracheal intubation, all groups showed further increases in HR and AP, with groups 3–5 (alfentanil 20–40 μg kg^{-1}) showing significant obtundation ($P<0.05$) of these increases compared with group 1. No patient in any group reported postoperative dysphoria or dissatisfaction with their anaesthetic. Ketamine 1 mg kg^{-1} with alfentanil 20–40 μg kg^{-1} provided statistically significant obtundation of the haemodynamic instability that is common with ketamine alone. (*Br. J. Anaesth.* 1998; **81**: 702–706).

Keywords: anaesthetics i.v., ketamine; analgesics opioid, alfentanil; anaesthetic techniques, induction; cardiovascular system, effects

Numerous agents and combinations of agents have been used in an effort to minimize haemodynamic instability during induction of anaesthesia.[1-8] Our recent study comparing thiopental (thiopentone), ketamine, thiopental with fentanyl and ketamine with fentanyl[9] demonstrated that the combination of ketamine and fentanyl provided haemodynamic stability during induction that was superior to the other three induction regimens, while at the same time providing excellent patient satisfaction.

When given alone, ketamine produces rapid induction but may cause unpleasant psychological side effects; ketamine also results in catecholamine release with subsequent tachycardia and hypertension.[10] Numerous medications, including midazolam and fentanyl,[9] have been shown to attenuate or prevent the hallucinations induced by ketamine, but while midazolam can significantly decrease the increase in arterial pressure (AP) normally seen after tracheal intubation when anaesthesia is induced with ketamine, midazolam provides little control of tachycardia after intubation.[11] Fentanyl has been shown to obtund the increase in both heart rate (HR) and AP after intubation with ketamine.[9]

Alfentanil has a more rapid onset and shorter duration of action than fentanyl,[12] properties which may be advantageous in short surgical cases where rapid induction is also desirable. However, at least one previous study has indicated that the ability of alfentanil to block increases in HR and AP during induction of anaesthesia is inferior to that of fentanyl.[13] If ketamine with alfentanil is haemodynamically stable, this regimen might offer an attractive alternative to more conventional techniques, such as thiopental alone or in combination with fentanyl.

Examining the hypothesis that a combination of ketamine and alfentanil (an induction regimen not reported previously in the literature) might also provide pleasant and haemodynamically stable induction of anaesthesia, and in an attempt to determine the optimum dose of alfentanil for this purpose, we studied HR, mean AP, surgical duration, length of stay in the recovery room and problems in the recovery room, including dysphoria, in association with induction of anaesthesia with ketamine alone and with ketamine and four different doses of alfentanil.

Patients and methods

After obtaining approval from both Institutional Human Studies Committees and written informed consent, we studied 100 patients, ASA I–II, undergoing elective surgery expected to last at least 30 min (greater than the expected duration of action of an induction dose of ketamine) and requiring general anaesthesia, including tracheal intubation. Power analysis showed that for an SD value of 15, alpha 0.05 and beta 0.2, a difference of 20 units (HR or AP) would be detected with 10 patients per treatment group, and for a difference of 10 units, 38 patients per treatment group would be required.

Patients were allocated randomly to receive one of five induction regimens according to a list prepared before the start of the study. Groups were compared after every 25 patients and the study was considered to be concluded when statistically significant differences between groups were found for both HR and AP. All patients with a history of cardiac disease, cerebrovascular disease, psychosis or recent drug abuse were excluded. No preoperative sedation was administered. Induction agents were administered and tracheal intubation was carried out by experienced residents or nurse anaesthetists who were

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aware of the agents and doses given. Drugs were prepared by the operating room pharmacist (Montefiore) or by the resident or nurse anaesthetist assigned to each patient (Northport VA). The study was conducted in a blinded manner in that neither patients nor study members recording data were aware of which technique was used. In cases where the assigned attending anaesthetist was a study team member, they recorded the induction data but were not informed of which technique had been used until induction was completed and all data recorded. In such cases, another attending anaesthetist was requested to be available but was not required to be physically present in the operating room.

Patients in group 1 received saline 10 ml, followed after 60 s by ketamine 1 mg kg^{-1}. Patients in groups 2–5 were given alfentanil 10, 20, 30 and 40 μg kg^{-1} (diluted with saline to 10 ml), respectively, followed after 60 s by ketamine 1 mg kg^{-1}. All patients received succinylcholine (suxamethonium) 1.25 mg kg^{-1} before tracheal intubation, at the point at which the patient became unresponsive to verbal commands and lost the eyelid reflex. All drugs were given as i.v. boluses. Laryngoscopy and tracheal intubation were begun 120 s after administration of ketamine. The lungs were ventilated with 100% oxygen by mask in the interval between administration of succinylcholine and laryngoscopy. If intubation could not be accomplished successfully within 30 s, the patient was dropped from the study and another patient substituted. After intubation, mechanical ventilation was instituted and anaesthesia maintained with nitrous oxide 4 litre min^{-1}, oxygen 2 litre min^{-1} and 1% isoflurane (Ohmeda modulus anaesthesia machines with Cyprane vaporizers, calibrated for accuracy by Ohmeda Corporation, Madison, WI, USA, every 12 months). At 5 min after intubation, induction was considered to be over and the anaesthetic management after this point was at the discretion of the anaesthesia team in charge of the case. During this 5 min, all surgical stimulation was avoided.

HR was monitored by electrocardiography (Physiocontrol Corp., Redmond WA, USA or Hewlett-Packard, Boise, ID, USA). Mean AP was measured oscillometrically using Dinamap monitors (Critikon, Tampa, FL, USA) capable of determining AP every 20–30 s. HR and AP were recorded at nine times: baseline, 60 s after administration of saline or alfentanil, 30, 60, 90 and 120 s after administration of ketamine, and 30 s, 60 s and 5 min after placement of the tracheal tube.

Age, sex, time spent in the recovery room and duration of surgery were recorded. Continuous end-tidal $P\text{CO}_2$ (Datascope Corp., Montvale, NJ, USA and Ohmeda) and oxygen saturation by pulse oximeter (Nellcor Co., Hayward, CA, USA and Ohmeda) were monitored during induction of anaesthesia to insure that haemodynamic instability, if present, was not caused by either hypoxia or hypercapnia. Patient complaints, dysphoria and adverse events in the recovery room were noted by the nurse assigned to each patient. Patients were discharged from the recovery room when they achieved an Aldrete score[14] of 8 (2 points possible for level of consciousness, respiration, overall level of activity, oxygen saturation and arterial pressure).

To normalize for variations in baseline values, data for HR and AP were compared as change from baseline between groups. Continuous data were analysed both within and between groups by two-way analysis of variance (ANOVA) for repeated measures. Changes from baseline to peak HR and AP were analysed by one-way ANOVA between groups. The Fisher–PLSD (protected least significant difference) test was used in all cases for multiple comparisons. Nominal data (incidence of nausea, dysphoria and patient complaints) were analysed using chi-square. In all cases, $P<0.05$ was considered statistically significant. Data for HR, AP, patient age, weight, surgical duration and time spent in the recovery room are reported as mean (SD).

Results

Three patients were excluded from the study because of difficulty with tracheal intubation. One patient was excluded because of arterial pressure cuff malfunction during induction and one patient was excluded because of i.v. line infiltration, not detected until after induction had begun. Fifty-four women and 46 men (100 patients in total) were studied.

All groups experienced increases in both HR (table 1, fig. 1) and AP (table 2, fig. 2) after administration of ketamine but before intubation ($P<0.05$), in addition to further increases in AP and HR after intubation ($P<0.05$). These increases were significantly obtunded ($P<0.05$) in groups 3–5 (ketamine with alfentanil 20, 30 and 40 μg kg^{-1}, respectively) compared with groups 1 and 2 (ketamine with saline and alfentanil 10 μg kg^{-1}, respectively). At 5 min after intubation, AP and HR were still increased above baseline ($P<0.05$) in groups 1 and 2, and in group 5 AP was slightly, but significantly, decreased compared with baseline.

No patient had oxygen saturation less than 95% at any time during the study. There were no statistically significant differences in end-tidal $P\text{CO}_2$ between the groups.

One patient in group 4 received atropine at 1–5 min after tracheal intubation for a heart rate of 38 beat min^{-1} not associated with hypotension. All patients were considered by their anaesthesia teams to be clinically stable during this time.

After surgery, the trachea was extubated in the operating room and all patients were taken to the recovery room with stable vital signs. No patient suffered emergence delirium or dysphoria or had any complaints regarding anaesthesia in the recovery room. One patient in group 3 was diagnosed as suffering from negative pressure pulmonary oedema in the recovery room (low oxygen saturation and positive chest x-ray findings), thought to be secondary to an episode of laryngospasm on emergence from anaesthesia. This patient's symptoms resolved over 3 h with mask oxygen and did not require re-intubation. There were no other intra- or postoperative complications apart from isolated instances of transient nausea (no statistically significant difference between groups).

Groups were similar in age, weight, duration of surgery and time spent in the recovery room after operation (table 3).

Table 1 Mean (SD) heart rate (HR) values in the five groups at nine times during the study (n=20 in each group). *P<0.05 from baseline within groups

	Time								
	Baseline	60 s after saline or alfentanil	30 s after ketamine	60 s after ketamine	90 s after ketamine	120 s after ketamine	30 s after intubation	60 s after intubation	5 min after intubation
Group 1 Ketamine 1 mg kg^{-1}	68(15.2)	64(16.1)	74(17.7)	78(23.0)*	84(23.4)*	94(23.0)*	106(24.7)*	103(22.4)*	93(17.0)*
Group 2 Ketamine + alfentanil 10 μg kg^{-1}	78(19.6)	83(24.7)	84(24.1)	90(23.4)*	97(22.4)*	103(27.2)*	117(24.2)*	110(23.9)*	87(19.2)*
Group 3 Ketamine + alfentanil 20 μg kg^{-1}	85(22.1)	85(18.5)	84(18.4)	88(20.9)	95(24.9)*	98(22.3)*	112(29.1)*	110(26.3)*	87(22.0)
Group 4 Ketamine + alfentanil 30 μg kg^{-1}	75(10.6)	75(12.6)	73(16.9)	79(16.0)	82(17.3)*	85(17.6)*	99(22.9)*	97(22.7)*	78(21.5)
Group 5 Ketamine + alfentanil 40 μg kg^{-1}	79(15.9)	77(17.1)	78(16.6)	80(16.4)	81(18.6)	86(20.3)*	102(25.3)*	95(22.7)*	76(22.0)

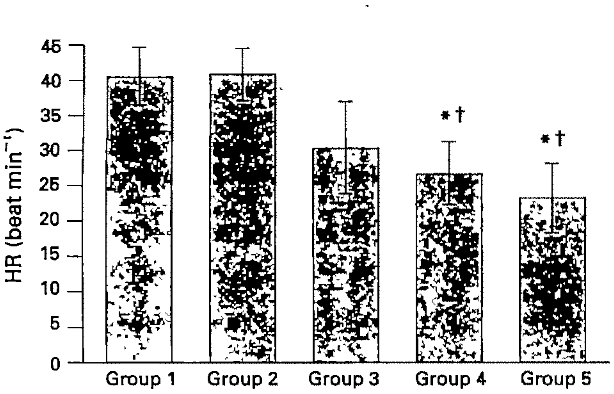

Figure 1 Maximum changes in heart rate (HR) from baseline after intubation for all five groups. *P<0.05 compared with group 1; †P<0.05 compared with group 2.

Discussion

All anaesthetic agents and induction combinations studied previously with respect to haemodynamic stability have been shown to have disadvantages. When added to thiopental, nitroprusside,[4] hydralazine[15] and isosorbide dinitrate[3] help to maintain stable AP after intubation but do not prevent (and may even cause) tachycardia. Propranolol and esmolol can prevent tachycardia after intubation but not hypertension, and can exacerbate bronchospasm and depress cardiac function.[1 16] Labetalol can provide control of both HR and AP,[17] but at the risk of cardiac depression and bronchospasm. Lidocaine (lignocaine), whether i.v. or topical,[5 6] has been shown to provide little protection against tachycardia or hypertension. Both fentanyl[18] and alfentanil[19] can cause chest wall rigidity, in addition to bradycardia and hypotension when given in doses sufficient to induce anaesthesia. Ketamine provides rapid onset and profound analgesia, but has been associated with hallucinations and catecholamine release, commonly resulting in both tachycardia and hypertension.[11]

Despite the recent increase in the popularity of propofol, thiopental is still the most common induction agent in all institutions of which we have personal knowledge. However, thiopental causes cardiac depression and venodilation. Our previous study,[9] performed in a patient population identical to that in

Table 2 Mean (SD) arterial pressure in the five groups at nine times during the study (n=20 in each group). *P<0.05 from baseline within groups

	Time								
	Baseline	60 s after saline or alfentanil	30 s after ketamine	60 s after ketamine	90 s after ketamine	120 s after ketamine	30 s after intubation	60 s after intubation	5 min after intubation
Group 1 Ketamine 1 mg kg^{-1}	98(10.4)	99(10.9)	100(13.5)	110(15.2)*	121(18.6)*	131(21.6)*	141(20.3)*	134(18.3)*	117(19.4)*
Group 2 Ketamine + alfentanil 10 μg kg^{-1}	95(12.7)	96(12.5)	101(11.4)	112(14.8)*	118(17.0)*	125(18.0)*	132(20.2)*	127(18.8)*	107(20.7)*
Group 3 Ketamine + alfentanil 20 μg kg^{-1}	101(13.9)	102(15.2)	98(16.4)	106(22.8)	113(22.3)*	115(24.3)*	123(19.7)*	119(21.6)*	102(18.7)
Group 4 Ketamine + alfentanil 30 μg kg^{-1}	97(11.8)	97(18.1)	96(14.7)	104(17.6)	110(16.6)*	114(16.5)*	124(23.5)*	119(20.4)*	96(28.3)
Group 5 Ketamine + alfentanil 40 μg kg^{-1}	98(14.3)	96(14.2)	96(13.6)	102(15.8)	103(13.7)	108(15.1)*	117(19.4)*	113(16.7)*	90(16.7)*

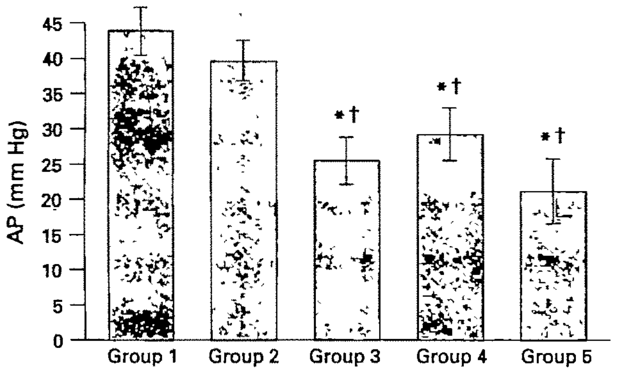

Figure 2 Maximum changes in arterial pressure (AP) from baseline after intubation for all five groups. *$P<0.05$ compared with group 1; †$P<0.05$ compared with group 2.

the current study, showed that thiopental, when given as the sole induction agent, typically resulted in large variations in both HR and AP. Thiopental does not result in direct release of catecholamines. However, HR and AP values after intubation following induction with thiopental proved to be no different from those achieved with ketamine, presumably because the lack of analgesia with this agent provided no protection against catecholamine release commonly caused by a noxious stimulus such as tracheal intubation. Thiopental with fentanyl provided partial protection against tachycardia and hypertension subsequent to intubation, but at the cost of both bradycardia and hypotension before intubation. Ketamine with fentanyl resulted in significant obtundation of tachycardia and hypertension after intubation, with little or no change in HR or AP before intubation.

The goal of our study was to determine if alfentanil in combination with ketamine could provide haemodynamically stable induction of anaesthesia, and to determine the optimum dose of alfentanil that would be required. We chose to evaluate ketamine with doses of alfentanil ranging from 10 to 40 μg kg^{-1} as this is the dose range of alfentanil that has been found previously to be at least partially effective in obtunding the haemodynamic response to tracheal intubation when combined with thiopental.[8,20] Ketamine is commonly administered for induction of anaesthesia in doses of 1–2 mg kg^{-1}. Previous studies have shown that catecholamine release and subsequent increases in HR and AP do not increase with increasing doses of ketamine but are constant within the range 0.5–1.5 mg kg^{-1}.[21] We chose to use ketamine 1 mg kg^{-1} for all patients in the hope that a lower dose would lead to a shorter duration of action, which would result in a lowered incidence of postoperative hallucinations and emergence delirium.

Our study clearly demonstrated that alfentanil, combined with ketamine, significantly obtunded the increase in HR and AP after intubation usually associated with ketamine alone, and greatly reduced the duration, without resulting in a decrease in HR and AP before intubation and causing only a small decrease in HR and AP within 5 min of intubation (alfentanil 40 μg kg^{-1} only). It must be noted, however, that statistically significant results are not necessarily clinically significant. Some patients with severe cardiac or cerebrovascular disease can tolerate little or no haemodynamic instability, while a reduction in the increase in HR and AP after intubation of approximately 14 beat min^{-1} and 20 mm Hg, respectively, combined with rapid return to baseline levels might mean a clinically significant difference in outcome for other patients. Changes in HR and AP responses with ketamine and alfentanil 30–40 μg kg^{-1} were comparable with those found in our previous study with either ketamine–fentanyl or thiopental–fentanyl.[9] The combination of thiopental–fentanyl is commonly administered and has been studied often.[7,22,23] As the onset times of both ketamine and alfentanil are 30–60 s,[12,24] in circumstances where a rapid onset of action with relative haemodynamic stability is required (i.e. rapid sequence induction in an elderly or debilitated patient), ketamine–alfentanil would seem to be a viable alternative to more traditional techniques.

Induction of anaesthesia with ketamine alone results in an increase in AP and HR after intubation that could be deleterious in patients with cardiac or cerebrovascular disease. We restricted our study to patients without cardiac or cerebrovascular disease, as we did not feel it medically safe to use ketamine as the sole induction agent in such patients. Consequently, we cannot say with absolute certainty that ketamine with alfentanil could provide superior haemodynamic stability in the more debilitated population; however, results obtained in previous studies with thiopental, ketamine and thiopental–fentanyl showed little difference in haemodynamic response between healthy patients and those with cardiac disease.[7,22,23,25–27] Therefore, it seems likely that this would also be the case for ketamine–alfentanil.

Benzodiazepines, barbiturates, potent inhalation anaesthetic agents[28,29] and fentanyl[9] reduce or eliminate the incidence of hallucinations and delirium caused by ketamine. We do not find it surprising, therefore, that our study, which included potent

Table 3 Age, weight, duration of surgery and recovery room time in the five groups (mean (SD or range)). No significant differences

	Group 1 Ketamine alone	Group 2 Ketamine + alfentanil 10 μg kg^{-1}	Group 3 Ketamine + alfentanil 20 μg kg^{-1}	Group 4 Ketamine + alfentanil 30 μg kg^{-1}	Group 5 Ketamine + alfentanil 40 μg kg^{-1}
Age (yr)	41.4(18–80)	40.0(19–80)	46.3(18–78)	43.8(21–68)	44.4(20–74)
Weight (kg)	79.6(13.4)	72.6(16.0)	74.3(17.0)	80.0(15.2)	81.5(20.6)
Case duration (min)	160(79.9)	186(117)	168(94.2)	162(82.3)	187(89.1)
Recovery room (min)	122(36.8)	135(95.8)	131(60.3)	121(38.2)	124(40.0)

inhalation agents in every case and alfentanil in most, showed no incidence of hallucinations, dysphoria or postoperative delirium.

In summary, induction of anaesthesia with ketamine and alfentanil 30–40 µg kg^{-1} provided haemodynamic stability superior to that obtained with ketamine alone and comparable with that seen in previous studies with either thiopental–fentanyl or ketamine–fentanyl, with little or no postoperative dysphoria or emergence delirium and no patient complaints regarding anaesthesia.

References

1. Vucevic M, Purdy GM, Ellis FR. Esmolol hydrochloride for management of the cardiovascular stress responses to laryngoscopy and tracheal intubation. *British Journal of Anaesthesia* 1992; **68**: 529–530.
2. Inada E, Cullen DJ, Nemeskal AR, Teplick R Effect of labetalol or lidocaine on the hemodynamic response to intubation: a controlled double-blind study. *Journal of Clinical Anesthesia* 1989; **1**: 207–213.
3. Hatano Y, Imai R, Komatsu K, Mori K. Intravenous administration of isosorbide dinitrate attenuates the pressor response to laryngoscopy and tracheal intubation. *Acta Anaesthesiologica Scandinavica* 1989; **33**. 214–218.
4. Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. *Anesthesia and Analgesia* 1979, **58**: 116–119.
5. Bachofen M. Suppression of blood pressure increases during intubation: lidocaine or fentanyl? *Anaesthesist* 1988; **37**: 156–161.
6. Stoelting RK. Circulatory response to laryngoscopy and tracheal intubation with or without prior oropharyngeal viscous lidocaine. *Anesthesia and Analgesia* 1977; **56**: 618–621.
7. Wang LP, Hermann C, Westrin P. Thiopentone requirements in adults after varying pre-induction doses of fentanyl. *Anaesthesia* 1996; **51**: 831–835.
8. Black TE, Kay B, Healy TEJ Reducing the haemodynamic responses to layryngoscopy and intubation. *Anaesthesia* 1984; **39**: 883–887.
9. Katz RI, Lagasse RS, Levy A, Alexander A. Hemodynamic stability and patient satisfaction after anesthetic induction with thiopental sodium, ketamine, thiopental–fentanyl and ketamine–fentanyl. *Journal of Clinical Anesthesia* 1993; **5**: 134–140.
10. Wilson RD, Traber DL, McCoy NR. Cardiopulmonary effects of CI-581—the new dissociative anaesthetic. *Southern Medical Journal* 1968; **61**: 692–696.
11. White PF. Comparative evaluation of intravenous agents for rapid sequence induction—thiopental, ketamine and midazolam. *Anesthesiology* 1982; **57**: 279–284.
12. Kay B, Cohen AT. Intravenous anaesthesia for minor surgery—a comparison of etomidate or Althesin with fentanyl or alfentanil. *British Journal of Anaesthesia* 1983; **55**: 165–171.
13. de Lange S, Stanley TH, Boscoe MJ. Alfentanil–oxygen anaesthesia for coronary artery surgery. *British Journal of Anaesthesia* 1981; **53**: 1291–1296.
14. Aldrete AJ, Krovlik D. The postanesthetic recovery score. *Anesthesia and Analgesia* 1970; **49**: 924–933.
15. Davies MJ, Cronin KD, Cowie RW. The prevention of hypertension at intubation: a controlled study of hydralazine on patients undergoing intracranial surgery. *Anaesthesia* 1981; **36**: 147–152.
16. McCammon RL, Hilgenberg JC, Stoelting RK. Effect of propranolol on circulatory responses to induction of diazepam–nitrous oxide anesthesia and to endotracheal intubation. *Anesthesia and Analgesia* 1981; **60**: 579–583.
17. Leslie JB, Kalayjian RW, McLomcghlin TM, Plachetka JR. Attenuation of the hemodynamic responses to endotracheal intubation with preinduction intravenous labetalol. *Journal of Clinical Anesthesia* 1989; **1**: 194–200
18. Waller JL, Hug CC jr, Nagle DM, Craven JM. Hemodynamic changes during fentanyl-oxygen anesthesia for aortocoronary bypass operation. *Anesthesiology* 1981; **55**: 212–217.
19. Ausems ME, Hug CC jr, de Lange S. Variable rate infusions of alfentanil as a supplement to nitrous oxide anesthesia for general surgery. *Anesthesia and Analgesia* 1983; **62**: 982–987.
20. Crawford DC, Fell D, Achola KJ, Smith G. Effects of alfentanil on the pressor and catecholamine responses to tracheal intubation. *British Journal of Anaesthesia* 1987; **59**: 707–712.
21. Zsigmond EK, Domino EF. Clinical pharmacology and current uses of ketamine. In: Aldrete JA, Stanley TH, eds. *Trends in Intravenous Anesthesia* Chicago· Year Book Medical Publishers, 1980; 283–330.
22. Cork RC, Weiss JL, Hameroff SR, Bentley J. Fentanyl preloading for rapid-sequence induction of anesthesia. *Anesthesia and Analgesia* 1984; **63**. 60–64.
23. Dahlgren N, Messeter K. Treatment of stress response to laryngoscopy and intubation with fentanyl. *Anaesthesia* 1981; **36**: 1022–1026.
24. Stoelting RK. *Pharmacology and Physiology in Anesthetic Practice*. Philadelphia: JB Lippincott, 1987; 136.
25. Fischler M, Dubois C, Brodaty D, Schlumberger S, Melchior JC, Guilmet D, Vourc'h G. Circulatory responses to thiopentone and tracheal intubation in patients with coronary artery disease. *British Journal of Anaesthesia* 1985; **57**: 493–496.
26. Prys-Roberts C, Greene LT, Meloche R, Foex P. Studies of anaesthesia in relation to hypertension II: haemodynamic consequences of induction and endotracheal intubation. *British Journal of Anaesthesia* 1971; **43**: 531–546.
27. Tweed WA, Mymin D. Myocardial force-velocity relations during ketamine anesthesia at constant heart rate. *Anesthesiology* 1974; **41**: 49–52.
28. Schultetus RR, Hill CR, Dharamraj CM, Banner TE, Berman LS. Wakefulness during cesarean section after anesthetic induction with ketamine, thiopental or ketamine and thiopental combined. *Anesthesia and Analgesia* 1986; **65**: 723–728.
29. Lagasse RS. Miscellaneous intravenous anesthetic agents. In: Katz RI, Vitkun SA, Eide TR, eds. *Pharmacology of Therapeutic Agents Used in Anesthesia: an Introduction.* Levittown, Pa: Pharmaceutical Information Associates, 1994; 69–77.

British Journal of Anaesthesia 1998; **81**: 707–712

Effect of i.v. ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery

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Summary

We studied 60 patients undergoing operation on the kidney with combined general and epidural anaesthesia, in a double-blind, randomized, controlled study. Patients were allocated to receive a preoperative bolus dose of ketamine 10 mg i.v., followed by an i.v. infusion of ketamine 10 mg h^{-1} for 48 h after operation, or placebo. During the first 24 h after surgery, all patients received 4 ml h^{-1} of epidural bupivacaine 2.5 mg ml^{-1}. From 24 to 48 h after operation, patients received epidural morphine 0.2 mg h^{-1} preceded by a bolus dose of 2 mg. In addition, patient-controlled analgesia (PCA) with i.v. morphine (2.5 mg, lockout time 15 min) was offered from 0 to 48 h after operation. Patients who received ketamine felt significantly more sedated at 0–24 h, but not at 24–48 h after operation, compared with patients who received placebo (P=0.002 and P=0.127, respectively). There were no significant differences in pain (VAS) at rest, during mobilization or cough, PCA morphine consumption, sensory block to pinprick, pressure pain detection threshold assessed with an algometer, touch and pain detection thresholds assessed with von Frey hairs, peak flow or side effects other than sedation. The power of detecting a reduction in VAS scores of 20 mm in our study was 80% at the 5% significance level. We conclude that we were unable to demonstrate an (additive) analgesic or opioid sparing effect of ketamine 10 mg h^{-1} i.v. combined with epidural bupivacaine at 0–24 h, or epidural morphine at 24–48 h after renal surgery. (*Br. J. Anaesth.* 1998; **81**: 707–712).

Keywords: anaesthetic techniques, epidural; anaesthetics i.v., ketamine; anaesthetics local, bupivacaine; analgesics opioid, morphine; pain, postoperative; surgery, urological

Ketamine has been used as an analgesic for more than 30 yr. For many years its mechanism of action was disputed but it is now generally agreed that one mechanism is specific binding to the phencyclidine site of the N-methyl-D-aspartate (NMDA) receptor ion channel.

In experimental studies, the NMDA receptor was found to play a significant role in injury-induced spinal hypersensitivity.[1] This sensitization of the central nervous system may account for significant postoperative pain.[2] The development of chronic neuropathic pain has also been related to activation of the NMDA receptor.[3–5] Experimental and clinical studies have demonstrated that block of the NMDA receptor before or during injury may prevent or reduce the development of central sensitization[6–15] and NMDA receptor block after injury can reduce or abolish central sensitization that has already been established.[16]

Previous studies indicate that NMDA receptor antagonists potentiate the effects of other analgesics, such as morphine,[17–20] local anaesthetics[21–24] and NSAID.[25] The mechanism of this potentiation may include reduced development of tolerance to opioids[26] and reduced tachyphylaxis to local anaesthetics.[21] As an NMDA receptor antagonist, ketamine may produce additive or synergistic effects with "balanced" treatment of postoperative pain.

The aim of our study was to investigate the effect of low-dose i.v. ketamine in combination with epidural bupivacaine and epidural morphine on pain and wound tenderness after renal surgery.

Patients and methods

We studied 60 patients undergoing elective nephrectomy or operation on pelvic structures (Hynes–Anderson operation), procedures with a similar lateral approach. Informed written consent was obtained from all patients and approval was obtained from the local Ethics Committee and the Danish National Board of Health. Patients were recruited from the Department of Urology, Skejby Sygehus, Aarhus University Hospital, during the period October 1994 to September 1996. Patients with a history of drug or alcohol abuse, chronic pain or daily intake of analgesics, with contraindications to insertion of epidural catheters, and those unable to cooperate, were not included.

The study was double-blind, randomized and placebo-controlled. The study drugs (ketamine 10 mg ml^{-1}) and placebo (isotonic saline) were prepared under sterile conditions by the hospital pharmacy in identical containers, marked with the name of the project, the investigator's name and consecutive patient numbers.

One hour before surgery, patients received diazepam 5–10 mg orally as premedication. Before

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induction of general anaesthesia, an epidural catheter was inserted between the T8–T9 interspace, and tested with lidocaine 20 mg ml^{-1} with epinephrine 3+2 ml. A bolus dose of 8 ml of bupivacaine 5 mg ml^{-1} was administered, followed by continuous infusion of 5 ml h^{-1} of bupivacaine 5 mg ml^{-1} throughout the operation, using a Pharmacia Deltec pump.

General anaesthesia was induced with fentanyl 0.2 mg, thiopental 3–7 mg kg^{-1} and midazolam 5 mg. Atracurium 0.5 mg kg^{-1} was used to facilitate orotracheal intubation, followed by infusion of atracurium 0.5 mg kg^{-1} h^{-1} for neuromuscular block. General anaesthesia was maintained with isoflurane up to a maximum of 1% and 66% nitrous oxide in oxygen. After induction of general anaesthesia, patients were allocated randomly to receive a bolus dose of ketamine 10 mg i.v. before surgical incision, followed by continuous i.v. infusion of ketamine 10 mg h^{-1} or placebo for 48 h after operation, using a Pharmacia Deltec pump. No other analgesics were administered during operation.

Infusion of dopamine 3 μg h^{-1} was started before surgery and continued throughout operation to optimize renal perfusion. Hypotension during and after operation was treated with i.v. infusion of isotonic sodium chloride, ephedrine 5 mg i.v. or increased doses of dopamine if considered necessary by the anaesthetist. Fluid and blood losses were replaced according to the standard prescriptions of the department. After operation, neuromuscular block was antagonized with glycopyrrolate 0.5 mg and neostigmine 2.5 mg. All patients were observed for at least 5 h after operation in the recovery unit.

POSTOPERATIVE ANALGESIA

For the first 24 h after surgery, patients received a continuous infusion of 4 ml h^{-1} of epidural bupivacaine 2.5 mg ml^{-1}. From 24 to 48 h after operation they received epidural morphine 0.2 mg h^{-1} preceded by a bolus dose of 2 mg. In addition, patients were offered patient-controlled analgesia (PCA) with morphine (2.5 mg, lockout time 15 min) for 0–48 h after operation, using a Pharmacia Deltec CADD-PCA ambulatory infusion pump. Except for ketamine–placebo, as described above, no other analgesics were administered.

POSTOPERATIVE RECORDINGS AND PAIN ASSESSMENTS

Pain scores on a visual analogue scale (VAS, 0 mm=no pain, 100 mm=worst pain imaginable) at rest, during mobilization from the supine to the sitting position and during cough were assessed by patients at 4, 6, 8, 22, 24, 26, 28, 30, 32, 46 and 48 h after operation. The number of PCA morphine doses used was recorded at the same times. Levels of sensory block to pinprick bilaterally were assessed at 4, 8 and 22 h after operation.

Pressure pain detection threshold was determined 2 cm caudal to the middle of the surgical incision with a hand-held electronic pressure algometer (Somedic AB, Sweden) before operation and at 6, 22, 30 and 46 h after operation. The stimulation probe has a circular tip of 6 mm (0.28 cm^2) and is connected to a pressure transducer built into the gun-shaped handle. The signal from the pressure transducer is amplified in a main unit, and the applied pressure is shown (in kPa) on a digital display. A display consisting of horizontal light bars indicates if the applied pressure is above or below a preset rate (20 kPa s^{-1} in this study). When the pressure pain detection threshold (defined as the minimal pressure (force) which induces pain) was reached, the subject was instructed to activate a push-button, which freezes the digital display. Three determinations with an interval of 30 s were made at each assessment, and a mean calculated.

Pain sensitivity was assessed before operation, and at 6, 22, 30 and 46 h after operation, with von Frey hairs, consisting of nine monofilaments (numbered 1–9) of variable diameter calibrated to deliver a specific force of 0.5–16 g on the skin. Touch detection threshold and pain detection threshold were assessed by applying von Frey hairs of increasing force to the skin 10 cm distal to the middle of the surgical incision. At the first test the region was marked. Patients were instructed to tell when touch was first detected, and when the stimulus became uncomfortable. If touch or pain detection thresholds exceeded 16 g (hair No. 9), this was registered with the No. 9.8. Each threshold was assessed three times, with an interval of 30 s and a mean calculated.

Peak flow (litre min^{-1}) was determined with a peak flow monitor (Spiropharma, Copenhagen) before operation, and at 6, 22, 30 and 46 h after operation with the patient in the sitting position. Three determinations with an interval of 30 s were made at each assessment and a mean calculated.

Side effects were recorded at 4, 6, 8, 22, 24, 26, 28, 30, 32, 46 and 48 h after operation. Sedation was assessed by patients using a visual analogue scale with the descriptors "fully awake" (0 mm) and "almost sleeping" (100 mm). Dreams were registered as none, pleasant or unpleasant. Nausea was registered as none, light, moderate or severe. The number of vomits (> 100 ml) was registered. Itching was registered as none, light, moderate or severe.

All assessments were made by three authors (S. I., L. N. and T. M. H.), with a maximum of two persons for each patient.

STATISTICAL ANALYSIS

The sample size was based on a power calculation which showed that 24 patients per group were necessary to achieve 80% power to detect a difference of 20 mm (VAS) in pain scores between patients treated with ketamine compared with placebo, with alpha=0.05 (two-tailed). Based on these values we decided to include 30 patients in each group.

Data are presented as medians, with upper and lower quartiles. Statistical analyses were performed using Fisher's exact test, the Mann–Whitney rank sum test for unpaired data and non-parametric two-way ANOVA for repeated measurements, where appropriate. If multiple testing was performed, significant *P* values were corrected with a Bonferroni test for repeated measurements. $P<0.05$ was considered statistically significant. Calculations were performed using Statgraphics Plus 7.0 under Windows 95, on a Pentium PC (150/LS-AWARD-PB/16M SIMM).

Table 1 Patient and operative data (median (lower and upper quartiles) or number). No significant differences

	Ketamine	Placebo
Sex (M/F)	(13/11)	(16/12)
Age (yr)	50 (43–68)	55 (50–65)
Height (cm)	175 (168–180)	172 (165–180)
Weight (kg)	75 (70–83)	75 (67–80)
Nephrectomy/Hynes–Anderson	19/5	26/2
Duration of surgery (min)	.175 (140–198)	150 (118–183)

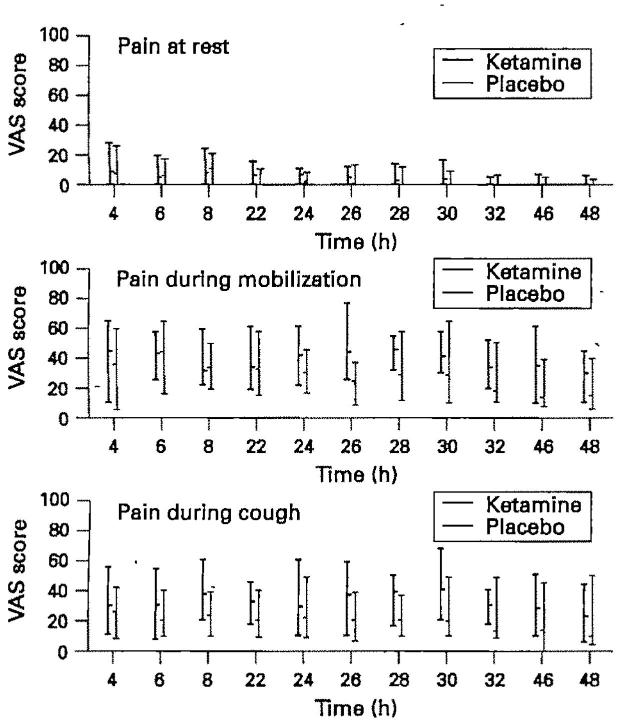

Figure 1 Median (upper and lower quartiles) visual analogue scale (VAS) pain scores during epidural infusion of bupivacaine 10 mg h^{-1} (0–24 h after surgery) and epidural infusion of morphine 0.2 mg h^{-1} (24–48 h after surgery) in patients who received ketamine 10 mg h^{-1} i.v. or placebo. Pain scores were assessed at rest, when moving from the supine to the sitting position and during cough. No significant differences between groups.

Results

Of the 60 patients studied, eight were excluded; therefore, there were 24 patients in the ketamine group and 28 in the placebo group. Reasons for exclusions were: displacement of the epidural catheter (two patients); change of operation type (two patients); wish to withdraw from the study (two patients); and inclusion criteria not fulfilled (two patients).

Patient characteristics and operative data are shown in table 1.

POSTOPERATIVE RECORDINGS AND PAIN ASSESSMENTS

There were no significant differences between groups for VAS scores at rest, during mobilization from the supine to the sitting position, or during cough at any time (P>0.05) (fig. 1). The number of PCA morphine doses used was not significantly different between groups at 0–24 h after operation (ketamine nine, placebo 12 doses; P=0.26) or at 24–48 h after operation (ketamine 2.5, placebo 3.5 doses; P=0.96).

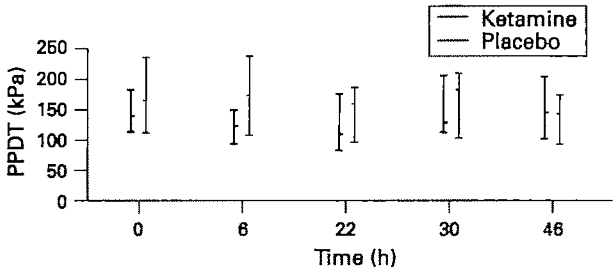

Figure 2 Median (upper and lower quartiles) pressure pain detection threshold (PPDT) 2 cm distal from the middle of the surgical incision in patients who received ketamine 10 mg h^{-1} i.v. or placebo. 0 h=Before surgery; 6 h and 22 h=during epidural infusion of bupivacaine 10 mg h^{-1}; 30 h and 46 h=during epidural infusion of morphine 0.2 mg h^{-1}. No significant differences between groups.

Table 2 Touch detection threshold determined with von Frey hair 10 cm distal to the middle of the surgical incision in patients receiving ketamine 10 mg h^{-1} i.v. or placebo. Von Frey hairs of increasing diameters were assigned increasing numbers, from 1 (0.5 g) to 9 (16 g). If touch or pain detection thresholds exceeded 16 g (hair No. 9), this was registered with the number 9.8. Values are median (lower and upper quartiles). No significant differences

	Ketamine	Placebo
Preop.	2.3 (2–3.3)	3 (2–3.7)
6 h postop.	3.9 (3–4.9)	4.5 (3–6)
22 h postop.	3.7 (3–5)	4 (3.3–6.3)
30 h postop.	3.3 (2.3–4)	3.3 (2.3–4)
46 h postop.	2.9 (2.3–3.7)	3.3 (2–4)

Table 3 Pain detection thresholds determined with von Frey hair 10 cm distal to the middle of the surgical incision in patients receiving ketamine 10 mg h^{-1} i.v. or placebo. Von Frey hairs of increasing diameters were assigned increasing numbers, from 1 (0.5 g) to 9 (16 g). If touch or pain detection thresholds exceeded 16 g (hair No. 9), this was registered with the number 9.8. Values are median (lower and upper quartiles). No significant differences

	Ketamine	Placebo
Preop.	6 (5.2–7.5)	5.3 (4.3–6.7)
6 h postop.	7.7 (6.7–9.8)	8.8 (6.2–9.8)
22 h postop.	7 (6–9)	7.7 (6.3–9.8)
30 h postop.	6.3 (5.3–8)	6.3 (5.3–9)
46 h postop.	6 (5.3–7)	5.7 (5–7.3)

The level of sensory block to pinprick was not different between groups at any time (P>0.21). The levels were between T4 and L2 in both groups.

There were no significant differences between groups for pressure pain detection thresholds (P>0.05) (fig. 2), von Frey hair touch and pain detection thresholds (P>0.23 for both thresholds) (tables 2, 3) or peak flow (P>0.5 for all assessments) at any time. The level of sedation was significantly higher in the ketamine group compared with the placebo group at 0–24 h after operation (P=0.002) but not at 24–48 h (P=0.127) (fig. 3). Two patients in the ketamine and one in the placebo group experienced psychomimetic side effects; one patient in each group had unpleasant dreams (P=0.55). There were no significant differences between groups for nausea (P>0.15), number of vomits (P>0.22) or itching (P>0.19).

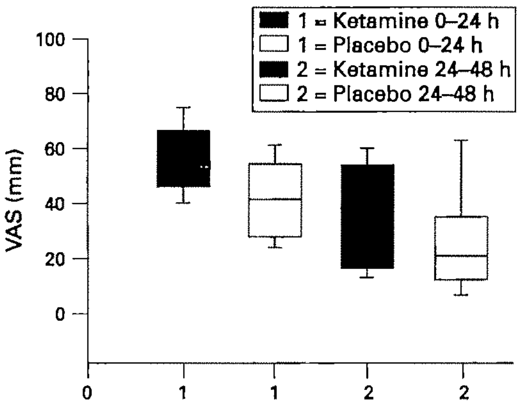

Figure 3 Median (upper and lower quartiles) visual analogue scale (VAS) sedation scores (0=fully awake, 100=almost sleeping) in patients who received ketamine 10 mg h^{-1} i.v. or placebo. 0–24 h=during epidural infusion of bupivacaine 10 mg h^{-1} (P=0.002); 24–48 h=during epidural infusion of morphine 0.2 mg h^{-1} (P=0.127).

Discussion

We found that patients who received ketamine 10 mg h^{-1} i.v. for 48 h after urological surgery felt significantly more sedated at 0–24 h after operation (during epidural analgesia with bupivacaine 10 mg h^{-1}), but not at 24–48 h after operation (during epidural analgesia with morphine 0.2 mg h^{-1}) compared with patients receiving placebo. There were no significant differences between groups in pain scores, PCA morphine consumption, sensory block to pinprick, pressure pain detection threshold and von Frey hair thresholds at surgical incision, peak flow or side effects. Consequently, we were unable to demonstrate additional analgesic (spinal) effects of low-dose i.v. ketamine in combination with epidural local anaesthetic or epidural morphine, but only mild supra-spinal effects (sedation).

Much of the pharmacological knowledge of the analgesic effect of ketamine is new, although the drug has been used for postoperative analgesia for several years. Only a few randomized, double-blind, placebo-controlled studies have been published.[19 20 22–24 27–34] Eight placebo-controlled studies investigated the effect of i.v. or i.m. ketamine on postoperative pain,[20 27–33] seven of which showed an analgesic effect. One of the first studies found that a single dose of ketamine 0.44 mg kg^{-1} i.m. produced analgesia with a mild degree of sedation and dizziness after orthopaedic surgery–laparotomy.[27] In another study, 60 patients were allocated randomly to receive either i.v. morphine 1 mg h^{-1}, ketamine 50 mg h^{-1} or placebo for 6 h after major, non-specified surgery. Morphine produced superior pain relief for the first 3 h, but ketamine was equally effective subsequently, and more effective than placebo.[28] I.v. ketamine (bolus of 30 mg followed by an i.v. infusion of 1 mg min^{-1} for 8 h) was compared with placebo during postoperative ventilator treatment after major abdominal surgery. The placebo group received significantly more supplementary analgesia than patients receiving ketamine.[29] Roytblat and colleagues found that the time to first request for morphine was increased and total demand for supplementary postoperative morphine was reduced when a single dose of ketamine 0.15 mg kg^{-1} i.v. was added to a standardized general anaesthetic in patients undergoing cholecystectomy.[30] Similar results were observed in Caesarean section patients where the time to first demand of morphine was increased and total morphine consumption over 24 h was reduced when general anaesthesia was induced with ketamine 1 mg kg^{-1} compared with induction with thiopental 4 mg kg^{-1}.[31] In a recent study of 20 patients undergoing nephrectomy, a bolus dose of ketamine 0.5 mg kg^{-1} i.v. followed by a continuous infusion of 2 μg kg^{-1} min^{-1} reduced pain and PCA morphine consumption during the first few postoperative hours compared with placebo. Further, hyperalgesia around the surgical wound was reduced 1, 3 and 7 days after operation in patients receiving ketamine.[32] Javery and colleagues[20] showed that addition of ketamine 1 mg ml^{-1} to morphine 1 mg ml^{-1} as i.v. PCA (1 ml with lockout period of 6 min) improved analgesia and reduced side effects compared with morphine 1 mg ml^{-1} alone.[20] Finally, morphine 1 mg h^{-1} with ketamine 5, 10 or 20 mg h^{-1}, or placebo, was given as an i.v. infusion for 24 h after upper abdominal surgery in 40 elderly patients. Ketamine did not significantly improve analgesia, but higher doses increased the incidence of postoperative dreaming.[33]

Varying doses of ketamine (4–30 mg) have been administered epidurally, but few were investigated in randomized, double-blind, placebo-controlled studies. One study found no improved analgesic effect of epidural ketamine compared with placebo[34] and another found ketamine to potentiate the analgesic effect of epidural morphine, but to have no analgesic effects on its own.[19] The combination of epidural ketamine and bupivacaine reduced onset time and increased the level of sensory block,[24] improved analgesia,[21] increased time to first analgesia and reduced analgesic consumption[22] compared with bupivacaine alone, or was found to have no effect on postoperative pain.[35]

The dose regimen chosen in our study was based on results from previous studies. Thus ketamine 0.15 mg kg^{-1} reduced secondary hyperalgesia caused by burn injury in human volunteers with acceptable side effects.[9] A single dose of ketamine 0.15 mg kg^{-1} reduced pain and analgesic requirements after cholecystectomy,[30] and Edwards and colleagues observed unacceptable side effects with doses of i.v. ketamine that were higher than 10 mg h^{-1}.[33]

I.v., and not epidural, administration was chosen in our study because the potential neurotoxic effect of long-term epidural infusion of ketamine has not been evaluated fully and ketamine has a local anaesthetic effect[36] which could interfere with the interpretation of our study. The postoperative regimen was designed to investigate if i.v. ketamine potentiated either epidural bupivacaine, epidural morphine, or both.

The dose and route of administration (i.v.) used in our study differed from previous combination studies with significant analgesic effects of ketamine. Thus in the studies with epidural local anaesthetic,[22–24 35] ketamine was administered epidurally in higher doses. Similarly, morphine and ketamine were administered epidurally in the study of Wong and colleagues[19] and this may explain the different results. Furthermore, the additional analgesic effect of ketamine in the above studies[19 22–24] could be related to a local anaesthetic effect of ketamine, and not necessarily to block of the NMDA receptor.

The results of our study are in agreement with those of Edwards and colleagues[33] and similar to those of Stubhaug and colleagues[32] where a comparable dose regimen of ketamine resulted in only a modest and short lasting effect on pain and analgesic consumption, and no effect on pressure pain thresholds at the wound site. Reduction of the area of mechanical hyperalgesia around the surgical wound on postoperative days 1, 3 and 7 observed by Stubhaug and colleagues in patients treated with ketamine may reflect reduced sensitization of central nociceptive neurones.[32] However, this did not lead to reduced pain intensity, as measured by VAS, or reduced morphine consumption, and the clinical implication of this finding remains to be evaluated.[32] We were unable to demonstrate any effects of ketamine on von Frey hair thresholds 10 cm from the surgical incision during epidural infusion with either bupivacaine or morphine. The discrepancy between our findings and those of Stubhaug and colleagues[32] may be because we investigated von Frey hair thresholds at some distance from the surgical wound and not at the area of hyperalgesia surrounding the wound. Thus a potential area of hyperalgesia around the wound in our patients may not have included the area where we performed our assessments.

In summary, an i.v. bolus dose and continuous infusion of ketamine did not reduce postoperative pain but increased side effects in the form of increased sedation during the first 24 h after operation. It is likely that a higher dose of i.v. ketamine would provide increased analgesia but it is not known if this could be achieved without unacceptable side effects.

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References

1. Dickenson AH. NMDA receptor antagonists as analgesics. In: Fields HL, Liebskind JC, eds. *Pharmacological Approches to the Treatment of Chronic Pain: New Concepts and Critical Issues (Progress in Pain research and Management, vol. 1.).* Seattle: IASP Press, 1994; 173–187.
2. Yaksh T. Epidural ketamine: A useful, mechanistically novel adjuvant for epidural morphine? *Regional Anesthesia* 1996; **21**: 508–513.
3. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; **52**: 259–285.
4. Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain* 1996, **67**: 69–77
5. Stannard CF, Porter GE. Ketamine hydrochloride in the treatment of phantom limb pain. *Pain* 1993; **54**: 227–230.
6. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-D-aspartate. *British Journal of Pharmacology* 1983; **79**: 565–575.
7. Davies SN, Lodge D. Evidence for involvement of N-methyl-D-aspartate receptors in "wind-up" of class 2 neurones in the dorsal horn of the rat. *Brain Research* 1987; **424**: 402–406.
8. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA-receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. *Neuropharmacology* 1987; **26**: 1235–1238.
9. Ilkjaer S, Petersen KL, Brennum J, Wernberg M, Dahl JB. Effect of systemic N-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans. *British Journal of Anaesthesia* 1996; **76**: 829–834.
10. Park KM, Max MB, Robinovitz E, Gracely RH, Bennet GJ Effects of intravenous ketamine, alfentanil, or placebo on pain, pinprick hyperalgesia, and allodynia produced by intradermal capsaicin in human subjects. *Pain* 1995; **63**: 163–172.
11. Arendt-Nielsen L, Petersen-Felix S, Fisher M, Bak P, Bjerring P, Zbinden AM. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo controlled experimental human study. *Anesthesia and Analgesia* 1995, **81**: 63–68.
12. Ilkjaer S, Dirks J, Brennum J, Wernberg M, Dahl JB. Effect of N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in man. *British Journal of Anaesthesia* 1997; **79**: 600–605.
13. Andersen OK, Felsby S, Nikolajsen L, Bjerring P, Jensen TS, Arendt-Nielsen L. The effect of ketamine on stimulation of primary and secondary hyperalgesic areas induced by capsaicin—A double blind, placebo-controlled, human experimental study. *Pain* 1996; **66**. 51–62.
14. Warncke T, Stubhaug A, Jørum E. Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1997; **72**: 99–106.
15. Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* 1994; **59**: 165–174.
16. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on the N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991; **44**· 293–299.
17. Chapman V, Dickenson AH. The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. *Brain Research* 1992; **573**: 321–323
18. Yamamoto T, Yaksh T. Studies on the spinal interaction of morphine and the NMDA antagonist MK-801 on the hyperesthesia observed in the rat model of sciatic mononeuropathy. *Neuroscience Letters* 1992; **135**: 67–70.
19. Wong CS, Liaw WJ, Tung CS, Su YF, Ho ST. Ketamine potentiates analgesic effect of morphine in postoperative epidural pain control. *Regional Anesthesia* 1996; **21**: 534–541
20. Javery KB, Ussery TW, Steger HG, Colclough GW Comparison of morphine and morphine with ketamine for postoperative analgesia. *Canadian Journal of Anaesthesia* 1996; **43**: 212–215.
21. Lee KC, Wilder RT, Smith RL, Berde CB. Thermal hyperalgesia accelerates and MK-801 prevents the development of tachyphylaxis to rat sciatic nerve blockade. *Anesthesiology* 1994; **81**: 1284–1293.
22. Cook B, Grubb DJ, Aldridge LA, Doyle E. Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. *British Journal of Anaesthesia* 1995; **75**: 698–701.
23. Naguib M, Sharif AMY, Seraj M, El Gammal M, Dawlatly AA. Ketamine for caudal analgesia in children: comparison with caudal bupivacaine *British Journal of Anaesthesia* 1991; **67**: 559–564.
24. Yanli Y, Eren A. The effect of extradural ketamine on onset time and sensory block in extradural anaesthesia with bupivacaine. *Anaesthesia* 1996; **51**: 84–86.
25. Price DD, Mao J, Lu J, Caruso FS, Frenk H, Mayer DJ. Effects of the combined oral administration of NSAIDs and dextromethorphan on behavioral symptoms indicative of arthritic pain in rats *Pain* 1996; **68**: 119–127.
26. Manning BH, Mao J, Frenk H, Price DD, Mayer DJ Continuous co-administration of dextromethorphan or MK-801 with morphine: attenuation of morphine dependence and naloxone-reversible attenuation of morphine tolerance. *Pain* 1996; **67**: 79–88.
27. Sadove MS, Shulman M, Hatano S, Fevold N. Analgesic effects of ketamine administered in subdissociative doses. *Anesthesia and Analgesia* 1971; **3**: 452–458.

28. Clausen L, Sinclair DM, van Hasselt CH. Intravenous ketamine for postoperative analgesia. *South African Medical Journal* 1975; **49**: 1437–1441.
29. Joachimsson PO, Hedstrand U, Eklund A. Low-dose ketamine infusion for analgesia during postoperative ventilatory treatment. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 697–702.
30. Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, Fisher A. Postoperative pain: The effect of low-dose ketamine in addition to general anesthesia. *Anesthesia and Analgesia* 1993; 77: 1161–1165.
31. Kee WDN, Khaw KS, Ma ML, Mainland P-A, Gin T. Postoperative analgesic requirement after cesarean section: A comparison of anesthetic induction with ketamine or thiopental. *Anesthesia and Analgesia* 1997; **85**: 1294–1298.
32. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiologica Scandinavica* 1997; **41**: 1124–1132.
33. Edwards ND, Fletcher A, Cole JR, Peacock JE. Combined infusions of morphine and ketamine for postoperative pain in elderly patients. *Anaesthesia* 1993; **48**: 124–127.
34. Kawana Y, Sato H, Shimada H, Fujita N, Ueda Y, Hayashi A, Araki Y. Epidural ketamine for postoperative pain relief after gynecologic operations: a double-blind study and comparison with epidural morphine. *Anesthesia and Analgesia* 1987; **66**: 735–738.
35. Weir PS, Fee JPH. Double-blind comparison of extradural block with three bupivacaine–ketamine mixtures in knee arthroplasty. *British Journal of Anaesthesia* 1998; **80**: 299–301.
36. Bion JF. Intrathecal ketamine for war surgery. A preliminary study under field conditions. *Anaesthesia* 1984; **39**: 1023–1028.

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Neonatal outcome and mode of delivery after epidural analgesia for labour with ropivacaine and bupivacaine: a prospective meta-analysis

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Summary

In this prospective meta-analysis, we have evaluated the effect of epidural analgesia with ropivacaine for pain in labour on neonatal outcome and mode of delivery compared with bupivacaine. In six randomized, double-blind studies, 403 labouring women, primigravidae and multiparae, received epidural analgesia with ropivacaine or bupivacaine 2.5 mg ml^{-1}. The drugs were administered as intermittent boluses in four studies and by continuous infusion in two. Apgar scores, neurological and adaptive capacity scores (NACS), degree of motor block and mode of delivery were recorded. The studies were designed prospectively to fit meta-analysis of the pooled results. Results showed similar pain relief and consumption of the two drugs. In the vaginally delivered neonates, NACS scores were approximately equal for both groups at 2 h, but at 24 h there were fewer infants with NACS less than 35 in the ropivacaine compared with the bupivacaine group (2.8% *vs* 7.6%; $P< 0.05$). Spontaneous vaginal deliveries occurred more frequently overall with ropivacaine than with bupivacaine (58% *vs* 49%; $P<0.05$) and instrumental deliveries (forceps and vacuum extraction) less frequently (27% *vs* 40%; $P<0.01$), while the frequency of Caesarean section was similar between groups. The intensity of motor block was lower with ropivacaine. There were no significant differences in adverse events. (*Br. J. Anaesth.* 1998; **81**: 713–717).

Keywords: anaesthetics local, ropivacaine; anaesthetics local, bupivacaine; analgesic techniques, epidural; analgesia, obstetric

Epidural administration of local anaesthetics, with or without opioids, is commonly used for the relief of pain in labour. Although effective and safe for the mother and fetus,[1 2] obstetric epidural analgesia may be associated with prolonged labour and increased incidence of instrumental deliveries and Caesarean section for dystocia.[3–6] This has been attributed to the reduced muscle power and relaxed pelvic diaphragm, which result from concomitant motor block.[2 5]

Ropivacaine is a new long-acting local anaesthetic, chemically homologous to bupivacaine and mepivacaine, but manufactured as the pure S-enantiomer, whereas the others are racemic mixtures. Preclinical studies demonstrated less central nervous and cardiovascular toxicity than with bupivacaine,[7] findings later confirmed in human volunteers.[8 9] The analgesic potency of ropivacaine is similar to that of bupivacaine, while motor block is less pronounced and of shorter duration.[7 10] This separation between motor and sensory block suggests that ropivacaine would be well suited for obstetric pain relief.

In this article we report a meta-analysis, based on the pooled results of six randomized, double-blind studies. The studies were designed prospectively to fit meta-analysis of neonatal outcome and mode of delivery, and to compare the efficacy and safety of epidural ropivacaine and bupivacaine 2.5 mg ml^{-1} when used for pain relief in labour[11–15] (note that Eddelston and colleagues[12] includes two studies). Objectives, variables to be compared and the studies included in the meta-analysis were specified in a formal protocol written before patient recruitment in any of the studies was finalized.

The main objective was to compare the effects of ropivacaine and bupivacaine on neonatal adaptation, evaluated by the neurological and adaptive capacity scores (NACS[16]) during the first 24 h of life. Secondary objectives included comparison of the effects of ropivacaine and bupivacaine on delivery outcome, measured by the frequency of spontaneous delivery, and incidence of instrumental deliveries and Caesarean section. Although current practice in most centres is to use low-dose bupivacaine with an opioid, this study compared the efficacy and profile of ropivacaine with that of bupivacaine, both without opioids.

The underlying six double-blind studies all showed that both drugs provided effective pain relief in labour.[11–15]

Patients and methods

After obtaining approval from the respective Research and Ethics Committees, we undertook six

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randomized, double-blind, multicentre studies of pain relief in labour with epidural ropivacaine or bupivacaine 2.5 mg ml^{-1}, administered in equal doses. Healthy, primigravid and multiparous ASA I or II women, aged 18–40 yr and in spontaneous active labour with a singleton fetus at term participated in the studies after giving written informed consent. Estimated fetal weight in all patients was at least 2500 g.

The study drug was administered epidurally either as intermittent bolus doses (top-ups) or as a continuous infusion. Epidural catheters were inserted via an appropriate lumbar interspace at L1–L4. In four studies, after excluding intravascular–subarachnoid placement of the epidural catheter, patients received 10 ml of epidural ropivacaine or bupivacaine 2.5 mg ml^{-1} in 5-ml aliquots. If necessary, an additional 5-ml dose was given to secure analgesia. Subsequent top-up doses of 10 ml were given on patient request at the investigator's discretion until delivery, or to a maximum of 8 top-ups (i.e. a maximum total dose of 237.5 mg). In two studies, the study drug was given by continuous infusion, after an initial dose of 10–15 ml. The infusion rate was adjusted within the range 6–12 ml h^{-1} to provide optimal pain relief, and supplementary boluses of up to 12 ml of study drug were given as needed at the investigator's discretion. The maximum total dose permitted in these studies was 450 mg in 24 h.

The study allowed subjects to receive pethidine (maximum 125 mg) for analgesia, at least 1 h before administration of the study drug. No concurrent analgesics, other than nitrous oxide, were allowed during the administration period, which lasted until delivery. Obstetric management was undertaken according to the clinical routines of each study centre, and participants received oxytocin for induction or augmentation of labour as indicated.

The following clinical assessments were made: Apgar scores at 1 and 5 min after birth, NACS at 2±0.5 h and 24±2 h after delivery, degree of maternal motor block and mode of delivery. NACS is a screening test to detect central nervous system depression caused by drugs and to differentiate such effects from those seen after birth trauma or perinatal asphyxia, or both. NACS assesses 20 criteria in five basic areas: active tone, adaptive capacity, general assessment, passive tone and primary reflexes. Each criterion is scored 0–2, depending on whether or not the neonate's response is absent or grossly abnormal (0), mediocre or slightly abnormal (1) or normal (2). A total NACS of 35–40 indicates a neonate not affected by drugs administered during labour.[16]

Neonates were excluded from NACS assessments if birth weight was less than 2500 g, if the mother had received other medications than those permitted in the protocol, and if they were delivered by Caesarean section or forceps delivery (other than outlet forceps or vacuum extraction).

Mode of delivery was recorded as normal (spontaneous vertex), forceps, vacuum extraction or Caesarean section. Motor block was assessed every 30 min until return of normal motor function, according to a modified, four-grade Bromage scale: 0=no motor block, 1=inability to raise extended legs (able to move knees and feet), 2=inability to flex knees (able to move feet only) and 3=complete paresis of leg and foot. The highest degree of motor block reached during the study was recorded for each patient.

Adverse events were defined as any unfavourable, unintended event (e.g. signs, symptoms) associated in time with administration of the study drug (including during the following 14 days), whether or not they were considered to be related to the drug. Adverse events were recorded during labour, daily during hospitalization and at follow-up by telephone 2–3 weeks after delivery. Adverse events were recorded separately for mother, fetus and neonate.

STATISTICAL ANALYSIS

At least 135 patients per treatment group were required to detect a difference of at least 2 points in total NACS between treatment groups (power of 90% and a significance level of 5%, assuming an SD of approximating 5 for both treatments). The variables analysed included: Apgar score at 1 and 5 min after delivery, NACS at 2 and 24 h, proportion of neonates with total NACS <35 at 2 and 24 h, proportion of patients (mothers, fetuses and neonates) with adverse events, and proportion of cases with a normal delivery, instrumental delivery (forceps and vacuum extraction) or Caesarean section. In addition, the proportion of patients with different maximum grades of motor block (0, 1, 2, 3) was analysed as a complement to the analysis of mode of delivery.

The Wilcoxon rank sum test, stratified for study, centre and parity, was used to detect differences between groups for Apgar scores, total NACS and the sum of scores for individual tests within each group of tests. The Mantel–Haenszel test, similarly stratified, was used for analysis of differences in proportions between treatment groups. That the tests were stratified means that the comparison between treatment groups was performed within stratum and the strata were thereafter weighed together to obtain the pooled results.[17] Each test of treatment differences was two-tailed, and $P<0.05$ was considered statistically significant.

Results

We studied 403 patients; 206 in the ropivacaine group and 197 in the bupivacaine group. Because of technical failure, five and six subjects in the ropivacaine and bupivacaine groups, respectively, were excluded. An additional patient in the latter group was excluded because she did not receive the study drug. The number of mothers and fetuses/neonates valid for analysis of drug consumption, patient characteristics and adverse events was therefore 201 and 190 in the ropivacaine and bupivacaine groups, respectively. In agreement with the previously described exclusion criteria, NACS was analysed in 147 neonates after ropivacaine analgesia and in 144 after bupivacaine; 199 ropivacaine recipients and 188 bupivacaine patients proved valid for analysis of Apgar score, mode of delivery and motor block.

Patient characteristics of the two groups were well matched, except for the number of patients who had undergone a previous Caesarean section (table 1). Nine women in the ropivacaine group and 15 in the bupivacaine group underwent a trial of vaginal birth after Caesarean section, however, this difference was

Table 1 Patient characteristics (mean (SD) [range] or number). *Previous Caesarean section: nine patients in the ropivacaine group and 15 in the bupivacaine group

	Ropivacaine (n=201)	Bupivacaine (n=190)
Age (yr)	28	27
	[16–41]	[16–41]
Height (cm)	165 (8)	164 (7)
	[145–184]	[150–179]
Weight (kg)	76 (11)	78 (12)
	[50–110]	[52–122]
Parity (n)		
Primiparae	125	115
Multiparae	76*	75*
ASA group (n)		
I	180	168
II	21	22

Table 2 Study drug consumption

	Ropivacaine 0.25% (n=201)	Bupivacaine 0.25% (n=190)
Top-up (ml)	(n=124)	(n=115)
Mean (SD)	34.9 (19.4)	38.1 (18.8)
Range	5.0–95.0	10.0–90.0
No. of doses (SD)	3.2 (2.0)	3.6 (1.9)
Continuous infusion (ml)	(n=77)	(n=75)
Mean (SD)	51.2 (23.2)	53.2 (27.6)
Range	11.5–111.1	12.0–135.0
Total mean (SD) dose mg	103 (55.8)	110 (59.5)
Mean (SD) (ml)	41.2 (22.3)	44.1 (23.8)
Range (ml)	5.0–111.1	10.0–135.0

Table 3 Duration of labour stages. *29 ropivacaine and 21 bupivacaine patients that underwent Caesarean section are excluded. Information regarding time to and duration of stage II is missing for two ropivacaine and two bupivacaine patients. **Information missing for one ropivacaine patient

	Ropivacaine (n=168)*	Bupivacaine (n=165)*
Time from main dose to stage II (h)		
Median	4.1	3.9
Range	0.25–13.8	0.1–13.4
Duration of stage II (h)		
Median	0.6	0.9
Range	0.0–4.1	0.0–5.8
Time from main dose to delivery (h)	(n=169)**	(n=167)**
Median	5.4	5.2
Range	0.1–14.8	0.4–13.4

Table 4 Mode of delivery. *P<0.05, **P<0.01

Mode of delivery	Ropivacaine (n=199)		Bupivacaine (n=188)	
Spontaneous vaginal	116	58.3%	92	48.9%*
Vacuum	26	27.1%	33	40.0%**
Forceps	28		42	
Caesarean section	29	14.6%	21	11.2%

not statistically significant. Pethidine was administered to 16 ropivacaine and 21 bupivacaine patients, before administration of the study drug, as permitted by the protocol. The amount of administered drug was similar between groups, with mean total doses of 103 mg for ropivacaine and 110 mg for bupivacaine, corresponding to 41.2 and 44.1 ml, respectively (table 2). Time from anaesthetic dose to delivery, and duration of labour were also similar between groups (table 3). There was no significant difference in oxytocin administration before delivery between the ropivacaine and bupivacaine groups (62 *vs* 59%, respectively).

At 1 min, median Apgar scores were 9 and 8 in the ropivacaine and bupivacaine groups, respectively; at 5 min, median scores were 9 in both groups. Two hours after delivery median NACS was 36 in both groups. There were 32 (21.8%) and 37 (25.7%) neonates with NACS <35 in the ropivacaine and bupivacaine groups, respectively (ns).

Twenty-four hours after delivery, median NACS were 38 and 37 in the ropivacaine and bupivacaine groups, respectively. Total NACS, active tone and capacity scores were all significantly higher in the ropivacaine group than in the bupivacaine group (P<0.05 for each comparison). Four neonates in the ropivacaine group (2.8 %) and 11 in the bupivacaine group (7.6%) had NACS <35 at 24 h (P<0.05).

A higher proportion of spontaneous vaginal deliveries occurred in the ropivacaine group compared with the bupivacaine group (58 *vs* 49%; P<0.05) (table 4). The proportion of instrumental deliveries, calculated as the sum of forceps deliveries and vacuum extractions, was smaller after ropivacaine than after bupivacaine (27 *vs* 40%; P<0.01). The overall percentage of patients who proceeded to Caesarean section did not differ between groups.

The proportion of multiparae was comparable in the ropivacaine and bupivacaine groups (38 *vs* 39%) (table 5). Significantly more patients among the multiparae in the bupivacaine group required instrumental delivery (28 *vs* 12%; P<0.05) and the frequency of spontaneous vaginal delivery was significantly higher in the ropivacaine group (80 *vs* 64%; P< 0.05) (table 5). Because of the skewed distribution between treatment groups with respect to the number of previous Caesarean sections, we undertook statistical

Table 5 Mode of delivery by parity, number of patients (%): 38% of ropivacaine patients and 39% of bupivacaine patients were multiparous

	Ropivacaine				Bupivacaine			
	Primigravidae		Multiparae		Primigravidae		Multiparae	
	(n=124)	%	(n=75)	%	(n=114)	%	(n=74)	%
Spontaneous	56	45	60	80	45	39	47	64
Instrumental	45	36	9	12	54	47	21	28
Caesarean section	23	19	6	8	15	13	6	8

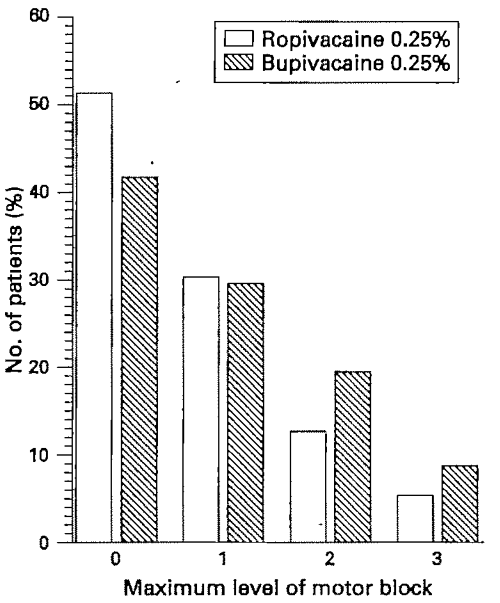

Figure 1 Maximum level of motor block (Bromage score) expressed as percentage of patients within groups. The overall degree of motor block was lower with ropivacaine ($P<0.05$).

analyses of delivery mode by stratifying subjects into those who had and had not undergone a previous Caesarean section. Among women who had had a previous Caesarean section, the frequency of spontaneous vaginal delivery was significantly higher in the ropivacaine group (78 *vs* 33%; $P<0.05$). Among those multiparae with no previous Caesarean section, 53 (80%) of the ropivacaine subjects and 42 (71%) of the bupivacaine recipients delivered spontaneously (ns).

The maximum degree of motor block was significantly less among the ropivacaine treated mothers than in the bupivacaine group ($P<0.05$). In the ropivacaine group, 51% of mothers had no measurable motor block (Bromage score=0) during the entire study compared with 42% in the bupivacaine group (fig. 1).

There were no significant differences in adverse events between groups. Among mothers in the ropivacaine group, hypotension was the most common adverse event, reported in 15% of cases, compared with 9.5% in the bupivacaine mothers (ns). Poor progression of labour was similar between groups (11% in the ropivacaine group *vs* 12% in the bupivacaine group; ns). Fetal bradycardia, classified as moderate or severe, occurred in 18% of ropivacaine cases and 19% of bupivacaine recipients. The incidence of jaundice, the commonest neonatal adverse event, did not differ between groups (9.5% and 10% for ropivacaine and bupivacaine, respectively).

Discussion

This meta-analysis focused primarily on the effects of epidural analgesia on neonatal outcome using the NACS assessment and mode of delivery. One implication of the stratified statistical analysis is that differences between individual studies and centres regarding drug administration, obstetric policy and hospital routines, for example, are eliminated, as treatment comparisons were performed within strata before the pooled results were obtained.

Our results showed a small advantage of ropivacaine, with fewer babies demonstrating NACS <35 at 24 h after birth compared with bupivacaine. Although this difference was significant, the clinical relevance of this observation is probably small. Amiel-Tison and colleagues[16] first described the NACS system for evaluating the effects of obstetric medication in full-term newborns in 1982. Whereas the early neonatal behavioural scale (ENNS), which preceded the NACS assessment and also evaluated the effects of maternal medication on neonates, concentrated on the newborn's habituation ability, in contrast, NACS places emphasis on motor tone as a key indicator of drug-induced abnormal neurobehaviour.[18]

No pharmacokinetic analysis was performed in our studies, but Datta and colleagues[19] undertook maternal pharmacokinetic analyses in women randomized to receive either ropivacaine or bupivacaine 150 mg (both as 30 ml of a 0.5% solution) for epidural anaesthesia for Caesarean section. They found that maternal $C_p$max was similar for ropivacaine and bupivacaine (1.3 and 1.1 mg litre^{-1}, respectively). However, the terminal half-life of ropivacaine in plasma was shorter than that for bupivacaine (5.2 *vs* 10.9 h). At delivery, mean unbound plasma concentrations of ropivacaine were approximately twice those of bupivacaine in both maternal and neonatal blood, but well below the concentration at which symptoms of maternal CNS toxicity might be expected.[9] All neonates in Datta's study had normal Apgar scores, acid–base values and NACS.

The significantly greater number of neonates with NACS >35 at 24 h after ropivacaine in our study may reflect a difference in the persistence of drug within the tissues of the neonate. Ropivacaine has lower lipid solubility and a shorter terminal half-life than bupivacaine.[7 19] Thus one can hypothesize that bupivacaine persists in the neonatal neural tissues longer than ropivacaine, such that its subtle changes on neurological function become evident at a time when the effects of ropivacaine have declined. This is supported by the lack of neurobehavioural differences at 2 h, which may suggest that both drugs exist within the neonatal nervous system to the extent that their effects are indistinguishable during the first hours after birth. Experimental support for this hypothesis was presented by Rosenberg, Kyttä and Alila who found considerably higher uptake of bupivacaine than ropivacaine in human epidural fat and rat sciatic nerves.[20] The differences in our study may therefore reflect the different physicochemical properties of the two local anaesthetics, and are not necessarily indicative of persistent adverse changes. The difference in NACS did not predict a less favourable outcome for the neonates in either group.

The use of ropivacaine was associated with a greater overall frequency of spontaneous deliveries and a lower percentage of instrumental deliveries (forceps and vacuum extractions) compared with bupivacaine. While it might be argued that the preponderance of bupivacaine multiparae who underwent instrumental delivery or Caesarean section skewed the results in favour of ropivacaine, we believe the observed differences between groups, and the consistent trend towards more spontaneous deliveries in all ropivacaine subjects, merit further study, with more standardized obstetric management.

As the infusion rates and top-up doses of the drugs in both groups were individually titrated to provide optimal pain relief, and total consumption of local anaesthetic was similar between groups, ropivacaine, on a dose-for-dose basis, was equieffective with bupivacaine in its analgesic properties. However, ropivacaine may be more suitable for analgesia in labour than bupivacaine because of its less pronounced motor block.

The less pronounced motor block in the ropivacaine group may have enabled more active participation and more effective bearing down, resulting in the increased incidence of spontaneous vaginal delivery. At the same time, a lesser reduction in the tone of the pelvic diaphragm might have enabled normal rotation of the fetal head during the second stage.[7,21] However, Russell and Reynolds, when comparing epidural labour pain relief with plain bupivacaine 1.25 mg ml^{-1} or bupivacaine 0.625 mg ml^{-1} with low-dose fentanyl or sufentanil could not demonstrate a difference in spontaneous deliveries between these groups, although motor block was significantly lower in the latter group.[22]

In this study, pain relief with epidural plain ropivacaine 2.5 mg ml^{-1} was found to be similar to that of plain bupivacaine 2.5 mg ml^{-1}. Recent studies with epidural infusions of ropivacaine 2 mg ml^{-1} alone, in doses of 4–10 ml h^{-1}, demonstrated that this solution also provides effective analgesia in labour at infusion rates of 6–8 ml h^{-1}.[23]

Ropivacaine is characterised by lower CNS and cardiovascular toxicity than bupivacaine at equal doses.[8,9] These qualities, and the results described above, suggest that ropivacaine is more suitable than bupivacaine for epidural analgesia in labour, and that further outcome studies, using more dilute solutions, should be undertaken.

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References

1. Abboud TK, Khoo SS, Miller F, Doan T, Henrikson EH. Maternal, fetal, and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine. *Anesthesia and Analgesia* 1982; **61**: 638–644.
2. Eddleston JM, Maresh M, Horsman EL, Young H, Lacey P, Anderton J. Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia. *British Journal of Anaesthesia* 1992; **69**: 154–158.
3. Chestnut DH, Vincent RD, McGrath JM, Choi WW, Bates JN. Does early administration of epidural analgesia affect obstetric outcome in nulliparous women who are receiving intravenous oxytocin? *Anesthesiology* 1994; **80**: 1193–1200.
4. Chestnut DH. Effect on the progress of labor and method of delivery. In Chestnut DH, ed. *Obstetric Anesthesia: Principles and Practice*. St Louis: Mosby Year Book, 1994; 403–419.
5. Howell CJ, Chalmers I. A review of prospectively controlled comparisons of epidural with non-epidural forms of pain relief during labor. *International Journal of Obstetric Anesthesia* 1992, **1**: 93–110.
6. Thorp JA, Parisi VM, Boylan PC, Johnston DA. The effect of continuous epidural analgesia on cesarean section for dystocia in nulliparous women. *American Journal of Obstetrics and Gynecology* 1989; **161**: 670–675.
7. McClure JH. Ropivacaine. *British Journal of Anaesthesia* 1996; **76**: 300–307.
8. Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesthesia and Analgesia* 1989; **69**: 563–569.
9. Knudsen K, Beckman M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *British Journal of Anaesthesia* 1997; **78**: 507–514.
10. Zaric D, Nydahl P-A, Philipson L, Samuelsson L, Heierson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0 25% bupivacaine on sensory and motor block in volunteers. A double-blind study. *Regional Anesthesia* 1996; **21**: 14–25.
11. Stienstra R, Jonker TA, Bourdrez P, Kuijpers JC, Van Kleef JW, Lundberg U. Ropivacaine 0.25% versus bupivacaine 0.25% for continuous epidural analgesia in labor: a double-blind comparison. *Anesthesia and Analgesia* 1995; **80**: 285–289.
12. Eddelston JM, Holland JJ, Griffin RP, Corbett A, Horsman EL, Reynolds F. A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour. *British Journal of Anaesthesia* 1996; **76**: 66–71.
13. Muir HA, Writer D, Douglas J, Weeks S, Gambling D, Macarthur A. Double-blind comparison of epidural ropivacaine 0.25% and bupivacaine 0.25%, for the relief of childbirth pain. *Canadian Journal of Anaesthesia* 1997; **44**: 599–604.
14. Gatt S, Crooke S, Lockley S, Anderson A, Armstrong P, Alley L. A double-blind, randomized, parallel investigation into the neurobehavioural status and outcome of infants born to mothers receiving epidural ropivacaine 0.25% and bupivacaine 0.25% for analgesia in labour. *Anaesthesia and Intensive Care* 1996; **24**: 108–109 (abstract).
15. Gaiser RR, Venkateswaren P, Persily EP, Buxbaum J, Cheek TG, Joyce TH, Gutsche BB. Comparison of 0.25% ropivacaine and 0.25% bupivacaine for epidural analgesia for labor and delivery. *Anesthesiology* 1995, **83** (Suppl. 3A): A949 (Abstract).
16. Amiel-Tison C, Barrier G, Shnider SM, Levinson G, Hughes SC, Stefani SJ. A new neurologic and adaptive capacity scoring system for evaluating obstetric medications in full-term newborns. *Anesthesiology* 1982; **56**: 340–350.
17. Hedges LV, Olkin I. *Statistical Methods for Meta-Analysis*. Orlando, FL: Academic Press, 1985; 1–12.
18. Zuckerman RL, Cornblath M. Neonatal assessment and resuscitation. In: Chestnut DH, ed. *Obstetric Anesthesia: Principles and Practice*. St Louis: Mosby-Year Book, 1994; 136–159.
19. Datta S, Camann W, Bader A, VanderBurgh L. Clinical effects and maternal and fetal plasma concentrations of epidural ropivacaine versus bupivacaine for Cesarean section. *Anesthesiology* 1995; **82**: 1346–1352.
20. Rosenberg P, Kyttä J, Alila J. Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into n-heptane, rat sciatic nerve, and human extradural and subcutaneous fat. *British Journal of Anaesthesia* 1986; **58**: 310–314.
21. Naulty JS. Epidural analgesia for labor. In: Norris MC, ed. *Obstetric Anesthesia*. Philadelphia: JB Lippincott, 1993; 319–340.
22. Russell R, Reynolds F. Epidural infusion of low-dose bupivacaine and opioid in labour. *Anaesthesia* 1996; **51**: 266–273.
23. Benhamou D, Hamza J, Eledjam J-J, Dailland P, Palot M, Seebacher J, Milon D, Heeroma K. Continuous extradural infusion of ropivacaine 2 mg/ml for pain relief during labour. *British Journal of Anaesthesia* 1997; **78**: 748–750.

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Quantitative and selective assessment of sensory block during lumbar epidural anaesthesia with 1% or 2% lidocaine

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Summary

We have examined sensory block during lumbar epidural anaesthesia using a cutaneous current perception threshold (CPT) sensory testing device in 20 patients who received 10 ml of either 1% or 2% lidocaine (lignocaine). CPT at 2000, 250 and 5 Hz stimulation at the trigeminal (V), ninth thoracic (T9) and second lumbar (L2) dermatomes, and dermatomal levels of block to light touch, temperature and pinprick discrimination were measured before and every 5 min until 60 min after epidural lidocaine. There were significant differences between 1% and 2% epidural lidocaine in all CPT at T9 and L2, in addition to maximal cephalad spread of the three sensory modalities. After 2% lidocaine, all CPT increased significantly at T9 and L2. In contrast, only at 250 and 5 Hz for L2 did epidural block with 1% lidocaine produce significant increases in CPT. Maximal level of loss of touch sensation after 1% lidocaine was significantly lower than that of cold and pinprick sensations. We conclude that the dose of lidocaine affected intensity of sensory block during lumbar epidural anaesthesia. In addition, differential neural block resulting from epidural anaesthesia appeared to be associated with a differential effect on nerve fibres of different sizes. (*Br. J. Anaesth.* 1998; **81**: 718–722).

Keywords: anaesthetic techniques, epidural; anaesthetics local, lidocaine; nerve, transmission

Despite a long history of use of epidural anaesthesia in clinical practice, the resultant sensory block has been assessed exclusively with the extent of loss of cold, pinprick and touch sensations. Most studies have relied on data obtained with these relatively crude measurements. Thus although it is generally thought that increasing dose of local anaesthetic produces denser block,[1–3] few, if any, quantitative examinations have been made to evaluate its density. In addition, epidural administration of local anaesthetic clinically results in zones of differential sensory block which are often described as loss of temperature discrimination and pinprick extending higher than that of light touch sensation.[4–6] Although this phenomenon has been attributed to varying degrees of block of nerve fibres of different size, little evidence exists to support this relationship.

Recently, it has become possible to perform quantitative and direct measurement of the functional integrity of sensory nerve fibres with the use of cutaneous current perception threshold (CPT) testing.[7 8] The electrical stimulus selectively excites distinct subpopulations of nerve fibres as a function of sinusoid frequency. Correlations between low-frequency stimulation and activation of small nerve fibres and between higher frequency stimulation and activation of large nerve fibres have been demonstrated with thermal perception threshold testing and quantitative vibration testing, respectively.[9] CPT are defined as the minimum amount of current applied transcutaneously that an individual consciously perceives.

In this study, we have quantitatively examined how lumbar epidural anaesthesia with 10 ml of 1% and 2% lidocaine (lignocaine) produces sensory block using a CPT testing device to see if a difference in dose of lidocaine alters the quality of epidural anaesthesia. In addition, we tested the hypothesis that a differential decrease in cold, pinprick and touch sensations is reflected by a differential effect of epidural lidocaine on the function of large and small nerve fibres.

Patients and methods

After obtaining approval from the Institutional Review Board and written informed consent, we studied 20 unpremedicated ASA I patients presenting for elective gynaecological surgery. None was taking regular medications or had evidence of neurological disease.

The study was performed in a quiet room on the day of surgery. Non-invasive arterial pressure, heart rate and pulse oximetry were monitored continuously throughout the study. After local anaesthesia with 0.1 ml of 1% lidocaine, i.v. infusion of acetated Ringer's solution was started in a hand or forearm vein at a rate of 10 ml h^{-1} kg^{-1}. Patients were then placed in the left lateral decubitus position, and the skin, subcutaneous tissue and supraspinous ligament anaesthetized with 2 ml of 1% lidocaine. The epidural space was identified using an 18-gauge Tuohy needle with the bevel directed cephalad via the midline approach at the L1–2 vertebral interspace, and a catheter (Portex) advanced 5 cm into the epidural space. The catheter was aspirated to exclude intrathecal or i.v. placement and then secured. The patient was then returned to the supine position.

Patients were trained to perceive perception

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thresholds to transcutaneous constant sine wave electrical currents at 2000, 250 and 5 Hz with a commercially available device (Neurometer CPT; Neurotron, Inc., Baltimore, MD, USA) before baseline measurements began. The current was delivered to the skin by a pair of 1-cm diameter gold surface electrodes that were separated by 1.7 cm with a clear Mylar spreader (Neurotron, Inc., Baltimore, MD, USA). The stimulating surface of each electrode was covered by a thin layer of electroconductive gel. CPT testing was performed at the trigeminal (V; in front of the ear), ninth thoracic (T9; above the umbilicus on the anterior axillary line) and second lumbar (L2; above the knee) dermatomes, on the left side, using the rapid screening procedure. Perception thresholds at each frequency were determined by increasing the current stepwise (controlled by the device) to a maximum of 9.99 mA until the patient reported sensation. The current was terminated and then repeated. The procedure for all three frequencies at all test sites required approximately 3–5 min.

Patients were allocated randomly to one of two equal groups to receive 10 ml of 1% lidocaine (group I) or 2% lidocaine (group II). After baseline measurements were obtained, patients were given the local anaesthetic via the epidural catheter, and the CPT and dermatomal levels of block to light touch, temperature and pinprick discrimination were measured every 5 min until 60 min after epidural lidocaine by an investigator blinded to the local anaesthetic solution injected. Loss of each sensory modality was determined by the patient's verbal response to the stimulus applied to the left anterior axillary line starting caudad and moving cephalad. The dull, hinged end of a sterile safety pin was used to examine light touch, an alcohol soaked swab for temperature and the sharp tip of a safety pin for pinprick.

Results are expressed as mean (SD) unless otherwise stated. CPT data were converted to %MPE, calculated as ((CPT value–baseline)/(cut-off–baseline))×100. Continuous variables, including CPT data, were compared using repeated measures ANOVA, and Dunnet or the Student's *t* test for *post hoc* testing. The Mann–Whitney test was used to determine differences in the maximum level of sensory block between groups, and the Friedman test and the Wilcoxon signed rank test with Bonferroni's adjustment were used for comparison between the three modalities in each group. $P<0.05$ was considered significant.

Results

Patient characteristics and baseline CPT did not differ between groups (table 1). All patients had CPT values within the normal range before administration of epidural lidocaine.

After epidural administration of 2% lidocaine, all CPT increased significantly at T9 and L2 (fig. 1). In contrast, only at 250 and 5 Hz for L2 did epidural block with 1% lidocaine produce significant increases in CPT. There were significant differences in all CPT at T9 and L2 between 1% and 2% epidural lidocaine, the latter producing higher %MPE. Neither solution had any effect on CPT at V. Epidural anaesthesia using 2% lidocaine produced significantly more extensive spread of sensory block to any modality than that with 1% lidocaine (fig. 2). Maximal level of loss of touch sensation was significantly lower than that of cold and pinprick sensations in group I.

Table 1 Patient characteristics and baseline current perception thresholds (mA) for each site tested (mean (SD or range)). No significant differences between groups

	Group I (n=10)	Group II (n=10)
Age (yr)	44.4 (37–49)	41.7 (20–56)
Weight (kg)	51.3 (4.5)	52.5 (8.6)
Height (cm)	157 (4)	155 (6)
Trigeminal		
2000 Hz	1.067 (0.370)	1.099 (0.369)
250 Hz	0.311 (0.152)	0.207 (0.123)
5 Hz	0.200 (0.140)	0.139 (0.117)
T9 (above umbilicus)		
2000 Hz	1.327 (0.415)	1.573 (0.460)
250 Hz	0.312 (0.107)	0.385 (0.126)
5 Hz	0.199 (0.121)	0.300 (0.252)
L2 (above knee)		
2000 Hz	0.889 (0.191)	0.800 (0.276)
250 Hz	0.307 (0.043)	0.312 (0.121)
5 Hz	0.162 (0.084)	0.213 (0.130)

There were no significant changes in arterial pressure, heart rate or pulse oximetry after epidural block with either lidocaine solution.

After completion of the study, all patients were given 10–15 ml of 2% mepivacaine which produced satisfactory anaesthesia for surgery.

Discussion

We have demonstrated that a difference in dose of lidocaine solution altered the quality of lumbar epidural anaesthesia. Together with more extensive spread of sensory levels, 10 ml of 2% lidocaine produced more intense sensory block than the same volume of 1% lidocaine, with CPT values increasing to a greater degree in patients given the former solution at all three frequencies. In addition, epidural anaesthesia with 1% lidocaine resulted in differential sensory block and a differential effect on nerve fibres of different sizes, as measured by a CPT monitor.

To our knowledge, this is the first comparative study demonstrating the intensity of sensory block of epidural anaesthesia. Previous studies investigating the effects of dose of local anaesthetic on the quality of epidural block focused on rate of onset, degree of motor block and duration. For example, Scott and colleagues[1] found that when similar volumes were administered, more concentrated bupivacaine and etidocaine solutions produced more rapid onset of sensory analgesia, greater frequency of adequate analgesia and longer duration of sensory block. Zaric and colleagues[3] showed that despite no difference in maximal median cephalad spread, duration of analgesia was significantly longer with 20 ml of 1% and 0.75% ropivacaine than with the same volume of 0.5% ropivacaine. The results of our study clearly showed that the larger dose of lidocaine produced not only more extensive spread of loss of cold, pinprick and touch sensations, but also more intense block of both large and small sensory nerve fibres.

Similarly, few clinical studies on differential block have examined the sensitivity of different nerve fibres to local anaesthetic other than maximal cephalad

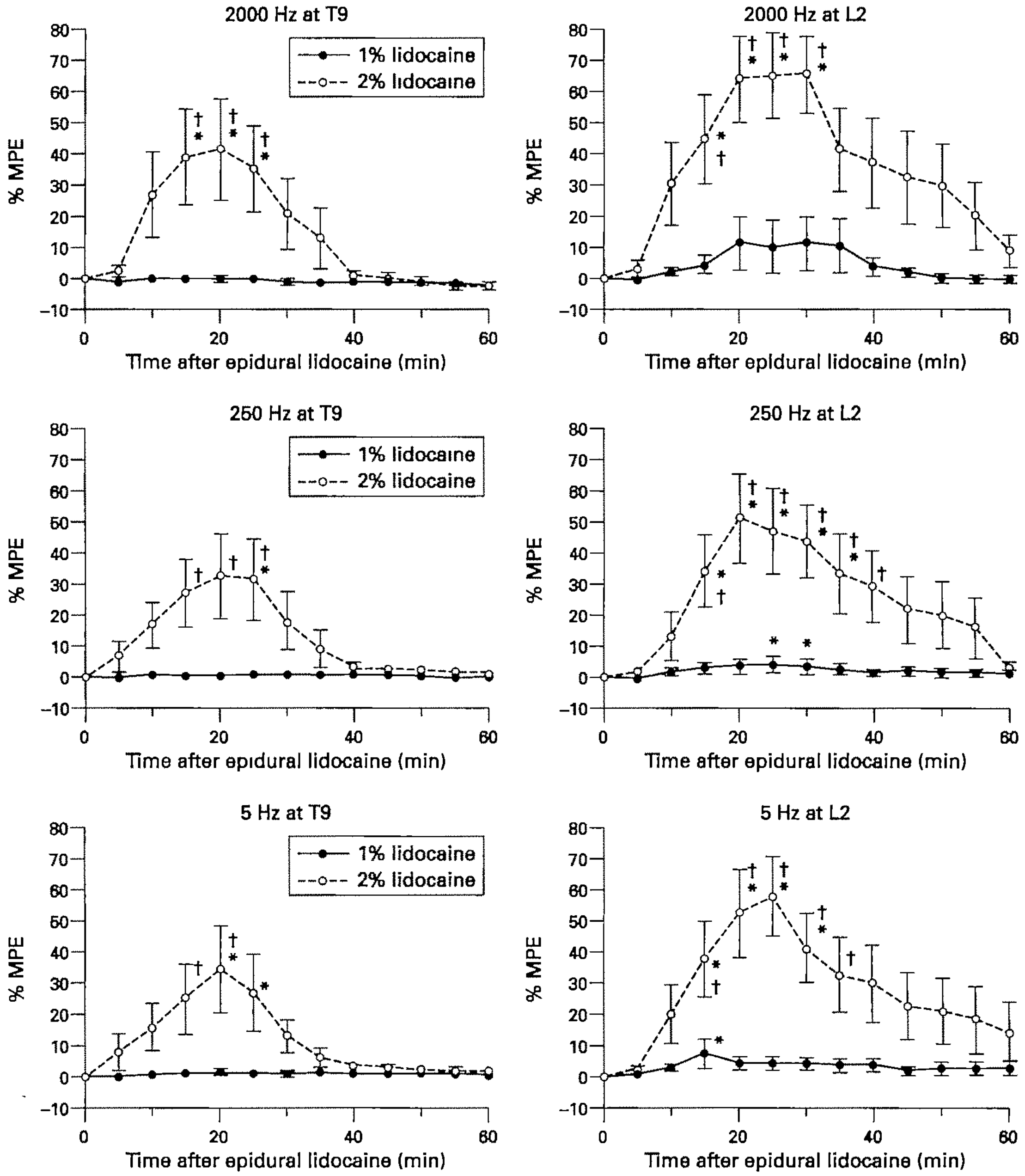

Figure 1 Time course of effect of epidural block with 10 ml of 1% or 2% lidocaine on current perception thresholds (CPT) at T9 and L2. The current perception threshold neurometer selectively stimulates Aβ, Aδ and C fibres using 2000-Hz, 250-Hz and 5-Hz stimuli, respectively. CPT values are expressed as percentage maximum possible effect (%MPE), where %MPE=((CPT value–baseline)/(cut-off–baseline))×100. Data are mean (SEM). *$P<0.05$ *vs* baseline, †$P < 0.05$ *vs* group I given 1% lidocaine.

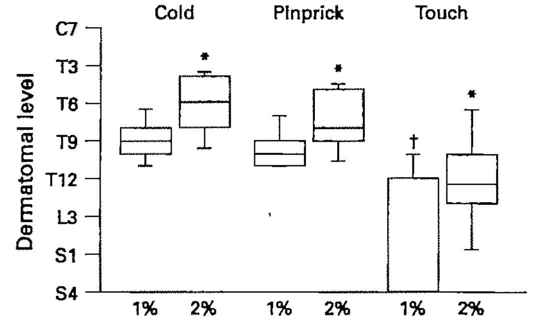

Figure 2 Maximal cephalad spread of epidural block with 10 ml of 1% or 2% lidocaine, as determined by loss of sensation to cold, pinprick and touch (n=10). Boxplot displays median and 10th, 25th, 75th and 90th percentiles for values. *$P<0.05$ *vs* group I given 1% lidocaine, †$P<0.05$ *vs* cold or pinprick sensation.

spread of sensory modalities. Brull and Greene[4] first reported the existence of zones of differential sensory block during epidural anaesthesia with 2% lidocaine. They found that the dermatomal level of anaesthesia to pinprick extended more cephalad than that to light touch, and the level of loss of cold sensation extended above that of pinprick. Stevens and colleagues[5] and White and colleagues[6] observed subsequently similar differential sensory block using these crude measurements. However, although it has been demonstrated that the sensibilities affected depend on activity in modality-specific primary afferent nerve fibres (i.e. loss of touch, pinprick and temperature sensibilities reflects the integrity of Aβ, Aδ and C fibres, respectively[10]) the relationships have never been examined in subjects given epidural anaesthesia. A recent study by Tay, Wallace and Irving[11] succeeded in measuring the intensity of epidural block with 10 ml of 2% lidocaine using a CPT monitor and demonstrated a significant increase in CPT values at only 5 Hz at the umbilicus. However, they failed to detect any relationship between the above crude measurements and different nerve fibres. Using the same technique, sensory block after lidocaine spinal anaesthesia was observed by Liu, Kopacz and Carpenter,[12] who demonstrated that recovery of CPT at 5, 250 and 2000 Hz was correlated with regression of sensory block to cold, pinprick and touch sensations. However, nerve block during epidural anaesthesia has been shown to occur differently and has been thought to involve different mechanisms from spinal anaesthesia.[13]

In our study, differential sensory block during lumbar epidural anaesthesia with 1% lidocaine was observed quantitatively and spatially. At L2, CPT at 2000 Hz, which are thought to reflect the function of large nerve fibres,[9] did not change, whereas 250 and 5 Hz stimuli, which have been shown to stimulate small nerve fibres, increased CPT significantly. This implies that there was a significant difference in the intensity of block between small and large nerve fibres. Maximal level of loss of touch sensation was significantly lower than that of cold and pinprick sensations, both of which were similar, indicating that the extent of block of nerve fibres that carry touch sensation appeared to be different from that of other nerve fibres. Taken together, these results suggest a relationship between clinical appearance of differential sensory block and differential effects on nerve fibres of different types during epidural anaesthesia; it is likely that the effects of epidural anaesthesia with lidocaine are more evident on small nerve fibres than on large ones.

Our observations conflict with the results of *in vitro* studies related to axon diameter. Measurements of compound action potential amplitude in segments of mammalian peripheral nerve have revealed that the large fast-conducting fibres are more susceptible to conduction block than are the smaller, slower-conducting fibres.[14,15] In addition, using mammalian dorsal root axons, Jaffe and Rowe[16] found no size-related differences in lidocaine sensitivity. Thus our observations of differential sensory block may depend on factors related only indirectly to axon diameter.

Although differences between fibre types in conduction safety and velocity,[17–19] state-dependent sodium channel block[20] and frequency-dependent block,[21] have been proposed as the mechanism of differential neural block, Fink's proposal[13] may offer a partial explanation for the differential effect of epidural lidocaine on nerve fibres. He hypothesized that the length of the nerve exposed to local anaesthetic is important for determining the extent of neural block. According to Tasaki,[22] at least three successive nodes of Ranvier must be blocked to cause neural transmission to fail. In the epidural space, large nerve fibres have fewer nodes exposed to local anaesthetics and, therefore, may be more resistant to conduction block than small fibres, in which more nodes should be exposed.

Examination of the three modalities and CPT testing did not reveal differential sensory block with 2% lidocaine. Because of the small number of patients studied, statistical power might have been insufficient to detect a significant difference in these variables. However, if Fink's hypothesis is true, one would expect to see a more obvious differential block in the upper thoracic region. As the effective bathed length of nerve roots decreases progressively along the spinal cord from sacral to cervical segments, upper thoracic and cervical roots may have a shorter exposure length to local anaesthetics. Thus CPT testing may have detected differential sensory block after epidural administration of 2% lidocaine with a test site at a dermatome higher than T9.

Another limitation of our study was the use of 10 ml of 1% lidocaine, which alone, epidurally, does not provide good anaesthesia for surgery. Thus differential effects on nerve fibres observed with this solution may not reflect differential neural block commonly seen during epidural anaesthesia.

In summary, using new technology involving electrical stimulation, our study demonstrated that the dose of lidocaine affected the intensity of sensory block during lumbar epidural anaesthesia. In addition, epidural anaesthesia may result in differential neural block.

References

1. Scott DB, McClure JH, Giasi RM, Seo J, Covino BG. Effects of concentration of local anaesthetic drugs in extradural block *British Journal of Anaesthesia* 1980, **52**: 1033–1037
2. Duggan J, Bowler GMR, McClure JH, Wildsmith JAW Extradural block with bupivacaine: Influence of dose, volume, concentration and patient characteristics. *British Journal of Anaesthesia* 1988, **61**. 324–331.
3. Zaric D, Axelsson K, Nydahl P-A, Philipsson L, Larsson P, Jansson JR Sensory and motor blockade during epidural analgesia with 1%, 0 75%, and 0 5% ropivacaine. A double-blind study. *Anesthesia and Analgesia* 1991; **72** 509–515
4. Brull SJ, Greene NM. Zones of differential sensory block during extradural anaesthesia. *British Journal of Anaesthesia* 1991, **66** 651–655.
5. Stevens RA, Bray JG, Artuso JD, Kao T-C, Spitzer L. Differential epidural block. *Regional Anesthesia* 1992, **17**: 22–25.
6. White JL, Stevens RA, Beardsley D, Teague PJ, Kao T-C. Differential epidural block: Does the choice of local anesthetic matter? *Regional Anesthesia* 1994; **19**· 335–338
7. Katims JJ, Long DM, Ng LKY. Transcutaneous nerve stimulation Frequency and waveform specificity in humans *Applied Neurophysiology* 1986, **49**· 86–91.
8. Chado HN. The current perception threshold evaluation of sensory nerve function in pain mangement. *Pain Digest* 1995; **5**: 127–134.
9. Pitei DL, Watkins PJ, Stevens MJ, Edmonds ME The value of the Neurometer CPT in assessing diabetic neuropathy by measurement of the current perception threshold. *Diabetic Medicine* 1994; **11** 872–876.
10. Mackenzie RA, Burke D, Skuse NF, Lethlean AK. Fibre function and perception during cutaneous nerve block *Journal of Neurology, Neurosurgery, and Psychiatry* 1975; **38**. 865–873.
11. Tay B, Wallace MS, Irving G. Quantitative assessment of differential sensory blockade after lumbar epidural lidocaine *Anesthesia and Analgesia* 1997; **84**: 1071–1075.
12. Liu S, Kopacz DJ, Carpenter RL. Quantitative assessment of differential sensory nerve block after lidocaine spinal anesthesia. *Anesthesiology* 1995; **82**: 60–63
13. Fink BR. Mechanisms of differential axial blockade in epidural and subarachnoid anesthesia. *Anesthesiology* 1989; **70** 851–858.
14. Gissen AJ, Covino BG, Gregus J. Differential sensitivities of mammalian nerve fibers to local anesthetic agents. *Anesthesiology* 1980; **53**: 467–474.
15. Wildsmith JAW, Brown DT, Paul D, Johnson S. Structure–activity relationships in differential nerve block at high and low frequency stimulation. *British Journal of Anaesthesia* 1989; **63**: 444–452.
16. Jaffe RA, Rowe MA. Differential nerve block Direct measurements on individual myelinated and unmyelinated dorsal root axons. *Anesthesiology* 1996; **84** 1455–1464.

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Incidence of bradycardia during recovery from spinal anaesthesia: influence of patient position

H. Ponhold and M. N. Vicenzi

Summary

We administered 0.5% plain bupivacaine 4 ml intrathecally (L2–3 or L3–4) in three groups of 20 patients, according to the position in which they were nursed in the post-anaesthesia care unit (PACU): supine horizontal, 30° Trendelenburg or hammock position (trunk and legs 30° elevated). Patients were observed until anaesthesia descended to less than S1. The incidence of severe bradycardia (heart rate <50 beat min^{-1}) in the PACU was significantly higher in patients in the Trendelenburg position (60%) than in the horizontal (20%, $P<0.01$) or hammock (10%, $P<0.005$) position. After 90 min, following admission to the PACU, only patients in the hammock position did not have severe bradycardia. In this late phase, the incidence of severe bradycardia in the Trendelenburg group was 35% ($P<0.005$) and 10% in patients in the supine horizontal position. In four patients, severe bradycardia first occurred later than 90 min after admission to the PACU. The latest occurrence of severe bradycardia was recorded 320 min after admission to the PACU. We conclude that for recovery from spinal anaesthesia, the Trendelenburg position should not be used and the hammock position is preferred. (*Br. J. Anaesth.* 1998; **81**: 723–726).

Keywords: anaesthetic techniques, subarachnoid; position, effects; heart, heart rate; complications, bradycardia

Moderate bradycardia occurs regularly during spinal anaesthesia.[1] The incidence of intraoperative severe bradycardia requiring therapy has been reported[2-4] and cardiac arrest has occurred.[5] However, there are no published data on the incidence of severe bradycardia during recovery from spinal anaesthesia.

Decreased venous return to the heart secondary to sympathetic block leads to a decrease in right atrial pressure and pressure in the great veins as they enter the right atrium; this is assumed to contribute to bradycardia during spinal anaesthesia.[6] The Trendelenburg position is associated with a higher venous return[7] which might result in a decreased incidence of severe bradycardia. The incidence and time of occurrence of severe postoperative bradycardia during recovery from spinal anaesthesia, and the influence of differences in venous return in the Trendelenburg, horizontal and hammock positions were examined in this study.

Patients and methods

We studied 60 patients, ASA I or II, undergoing arthroscopy of the knee under spinal anaesthesia after obtaining approval from the Ethics Committee of the Faculty of Medicine, University of Graz, Austria and written informed consent from all patients. Patients with characteristics known to influence the incidence of intraoperative severe bradycardia from spinal anaesthesia were excluded (i.e. heart rate (HR) <60 beat min^{-1}, age >50 yr and <20 yr, ASA >II, cardiovascular disease or medication with β-adrenergic blocking drugs).[3 4] Pregnancy was also an exclusion criterion.

All patients received oral premedication with midazolam 7.5 mg, 1 h before induction of spinal anaesthesia. Continuous monitoring in the operating theatre and in the post-anaesthesia care unit (PACU) consisted of ECG, HR and pulse oximetry, in addition to non-invasive systolic and diastolic arterial pressure measurements (every 5 min). Data were recorded automatically onto a computer using Hewlett Packard DocVue. In the operating theatre, patients received i.v. infusion of 6% hydroxyethylstarch 500 ml before induction of spinal anaesthesia. This was followed by slow infusion of Ringer's solution 500 ml. Plain bupivacaine 0.5% (4 ml) was injected into the subarachnoid space at L2–3 or L3–4 with the patient in the lateral horizontal position. After injection of local anaesthetic, the patient was immediately positioned horizontally and supine for surgery.

Severe bradycardia was defined as HR <50 beat min^{-1} requiring treatment with atropine 0.5 mg i.v., repeated as necessary. Severe hypotension was defined as a decrease in systolic arterial pressure (SAP) to less than 70% of the patient's initial SAP before induction of spinal anaesthesia, requiring treatment with ephedrine 25 mg i.v. Moderate bradycardia and moderate hypotension were defined as statistically significant decreases in these variables not requiring treatment.

After surgery, patients were transferred to the PACU and allocated randomly to one of three groups of 20 patients each according to the position in which they were to be nursed in the PACU: horizontal supine, hammock (legs and trunk 30° elevated) or 30° Trendelenburg. Randomization was accomplished by predetermined numbers; in the operating

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theatre both the patient and examiner were blinded to group allocation; in the PACU, this was not possible because the position of the patient was obvious. Monitoring and therapy continued as before. The dermatomal level of anaesthesia (no sensation to pinprick with the sterile tip of a safety pin after a strong push onto the skin) was recorded at the time of admission to the PACU and at 15-min intervals. Patients remained in the PACU until anaesthesia descended to below S1. Duration of spinal anaesthesia was defined as the time between intrathecal injection of bupivacaine and the moment when the anaesthetic level had descended to below S1.

Data are expressed as number, percentage, mean or median (SD, confidence limits or percentile). Comparisons of several means and continuous data were made using two-way ANOVA, and chi-square analysis with the Bonferroni–Dunn procedure. Exact binominal confidence limits were used for comparison of incidents. $P<0.05$ was considered statistically significant. The statistical computer package used was NCSS 97, except for the prospective power analysis, where PASS 6.0 was used; both were run on Win NT 4.0 Workstation using a Pentium PC.

Results

There was no significant difference in mean age, weight, height, sex ratio or ASA status between the three groups (table 1). All patients had satisfactory block for surgery and did not require supplementary medication. Median level of anaesthesia at the time of admission to the PACU was L3 (25th –75th percentile: L2–L4) in all groups. There was no significant difference in duration of spinal block or duration of stay in the PACU (table 1). During the observation period, no patient had an oxygen saturation less than 95%; oxygen was not administered to any patient. No patient fell asleep or had respiratory obstruction.

Table 1 Comparison of patient characteristics (mean (SD or range) or number). Initial=before induction of spinal anaesthesia, SAP=systolic arterial pressure, DAP=diastolic arterial pressure, duration of spinal block=time from intrathecal injection of bupivacaine to the moment when the anaesthetic level decreased to below S1, PACU=post-anaesthesia care unit, ISB=intraoperative severe bradycardia (HR <50 beat min^{-1}), ISH=intraoperative severe hypotension (SAP <70% of initial value)

	Hammock position (n=20)	Horizontal position (n=20)	Trendelenburg position (n=20)
Sex (M/F)	8/12	7/13	11/9
Age (yr)	40 (21–47)	37 (26–50)	36 (20–50)
Height (cm)	171 (11)	172 (10)	169 (10)
Weight (kg)	73 (11)	76 (11)	71 (12)
ASA	1.2 (0,3)	1.2 (0,4)	1.3 (0,2)
Initial heart rate (beat min^{-1})	73.8 (8.1)	74.3 (9.1)	73.7 (9.3)
Initial SAP (mm Hg)	130.9 (16,1)	133.0 (14,5)	131.8 (21,5)
Initial DAP (mm Hg)	69.0 (11,3)	72.5 (10,7)	67.8 (14,5)
Duration of spinal block (min)	320 (86)	308 (52)	325 (56)
Duration of stay in PACU (min)	212 (56)	196 (53)	225 (19)
No. of patients with ISB	2	2	2
No. of patients with ISH	1	1	0

Table 2 Number of patients with bradycardia (number (95% CI)) in the post-anaesthesia care unit (PACU). *During total stay in the PACU: overall chi-square $P<0.001$; pairwise comparisons, Trendelenburg *vs* horizontal position $P<0.01$ and Trendelenburg *vs* hammock position $P<0.005$. **Later than 90 min after admission to the PACU: overall chi-square $P<0.01$; pairwise comparison, Trendelenburg *vs* hammock position $P<0.005$

	Hammock position (n=20)	Horizontal position (n=20)	Trendelenburg position (n=20)
During total stay in PACU	2 (1.2–31.7%)	4 (5.7–43.7%)	12 (36.1–80.9%)*
Later than 90 min after admission to PACU	0 (0–16.8%)	2 (1.2–31.7%)	7 (15.4–59.2%)**

In the operating theatre, all patients were in the horizontal supine position, where two patients in each group had an episode of severe bradycardia (table 1). In the PACU, patients in all groups had moderate bradycardia, and this continued until the end of the observation period. Between groups, however, there was no difference in the mean decrease in HR. In the PACU, there was significant variation in the incidence of severe bradycardia in terms of incidence during the total stay in the PACU and incidence later than 90 min after admission to the PACU (table 2).

The time of occurrence of severe bradycardia in the PACU and anaesthetic level at which it occurred are documented in figure 1. After successful treatment of severe bradycardia during the first 90 min after admission to the PACU, some patients continued to have episodes of severe bradycardia, with the latest occurring after 320 min. In one patient in the horizontal group and in three patients in the Trendelenburg group, an episode of severe bradycardia occurred later than 90 min after admission to the PACU where none had occurred previously; one patient had his first episode of severe bradycardia 255 min after admission to the PACU.

Both patients in the Trendelenburg group who had severe bradycardia in the operating theatre also had severe bradycardia in the PACU; none of the patients with intraoperative severe bradycardia in the other groups (two patients in each group) had severe bradycardia in the PACU. All patients with intraoperative severe bradycardia were treated successfully with atropine 0.5 mg. One patient in the hammock group and one patient in the horizontal group had intraoperative severe hypotension, treated successfully with ephedrine 0.25 mg (table 1). On admission to the PACU, the HR of all patients treated in the intraoperative period with atropine or ephedrine was below the initial value before induction of spinal anaesthesia. Neither of the two patients with intraoperative severe hypotension had severe hypotension or severe bradycardia after operation. The number of patients with intraoperative severe bradycardia or intraoperative severe hypotension, however, was insufficient for statistical analysis on the influence of intraoperative use of atropine or ephedrine on the incidence of severe bradycardia in the PACU. All patients with intraoperative severe bradycardia or intraoperative severe hypotension were included in the PACU analysis.

In the PACU, mean SAP was lower than the initial

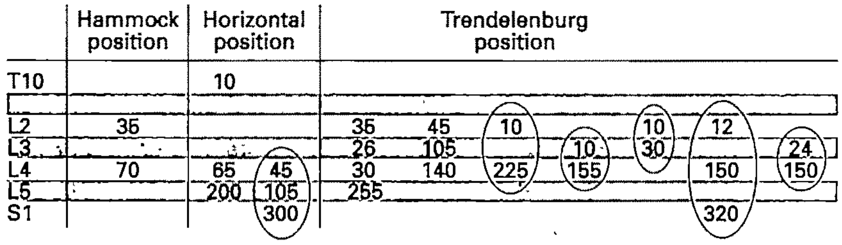

Figure 1 Time of occurrence of severe bradycardia (HR <50 beat min^{-1}) in the post-anaesthesia care unit (PACU), expressed as minutes after admission to the PACU, level of anaesthesia at the time of occurrence and position of the patient. Encircled numbers represent the time of occurrence of recurrent episodes of severe bradycardia in single patients. Numbers without a circle represent the time of occurrence of severe bradycardia in patients with only one episode of severe bradycardia.

value before induction of spinal anaesthesia and remained so until the end of the observation period. However, severe hypotension requiring therapy did not occur in the PACU. Between groups there was no difference in mean changes in SAP. There was no difference between mean diastolic arterial pressure in the PACU and pre-induction values in any group.

Discussion

In the operating theatre, where all patients were in the supine horizontal position, the incidence of severe bradycardia did not differ between groups, and was similar to previous studies.[2-4] We can assume that the risk factors for severe bradycardia during spinal anaesthesia were evenly distributed between groups.

For comparison with previous studies,[2-4] we defined severe bradycardia as HR <50 beat min^{-1}. This value was thought to be an appropriate end-point for intervention in this carefully defined group of patients: other patients may require earlier intervention or may safely tolerate this HR. Similar numbers of patients in the three groups were treated with atropine and ephedrine in the operative period and it is unlikely that these treatments influenced the differences in the incidence of bradycardia between groups.

In the PACU, patients in the 30° Trendelenburg position had a higher incidence of severe bradycardia than patients in the horizontal or hammock position. This observation seems to contradict the proposed mechanisms for bradycardia during spinal anaesthesia: according to Greene,[8] diminished venous return secondary to sympathetic block activates great vein and right atrial cardiac receptors that both, by reflex mechanisms and directly, slow the HR. Although patients in the Trendelenburg position have greater venous return,[7] they had a higher incidence of severe bradycardia. The level of moderate bradycardia did not differ between groups in our study. Therefore, a decrease in venous return most probably was not the primary cause for moderate or severe bradycardia during spinal anaesthesia in our patients.

In patients with higher levels of sympathetic block, including levels T1–4, cardiac accelerator denervation also slows HR.[9] In our patients, moderate bradycardia in the PACU continued until the end of the observation period with an anaesthesia level below S1 more than 5 h after subarachnoid injection of bupivacaine. Cardiac accelerator block most probably did not play a role in the mechanism of bradycardia in the PACU. Assuming a differential block of six segments between sensory and sympathetic block[10] only one patient had a sensory level high enough to block one cardiac accelerator segment at the time of admission to the PACU. In the later phase of recovery it can be assumed that no patient had cardiac accelerator block at a time when all patients had moderate bradycardia, and when some had episodes of severe bradycardia.

Recent studies using HR variability demonstrated modulation of sympathovagal balance during spinal anaesthesia.[11 12] During the onset of spinal anaesthesia, disruption of sympathetic neural pathways leads to a decrease in sympathetic activity and a reflex reduction in parasympathetic activity. Over time, reflex parasympathetic inhibition is withdrawn. Although in volunteers without spinal block, the autonomic system attempts to maintain sympathovagal balance,[13] 30 min after spinal injection, decreased sympathetic activity and increased parasympathetic activity in the cardiac autonomic nervous system were observed. As acetylcholine released at the vagal nerve endings diminishes the release of norepinephrine from neighbouring sympathetic terminals,[14 15] decreased cardiac sympathetic activity could be the result of both direct and indirect effects.

Studies of the influence of the Trendelenburg position in volunteers without spinal anaesthesia have not shown an effect on HR.[7 16] Furthermore, the Trendelenburg position in volunteers without spinal anaesthesia is not associated with significant alteration of dominant parasympathetic cardiac control in comparison with the resting supine position.[17] However, increased venous return in a patient under spinal anaesthesia with coexisting decreased sympathetic and increased parasympathetic activity could have a different effect compared with volunteers with normal sympathovagal balance and a tendency to maintain this balance.[13]

Time from injection until the anaesthetic level descended to below S1 was more than 5 h. As moderate bradycardia continued until this time, and some patients also had episodes of severe bradycardia after 5 h, we can assume that sympathovagal imbalance was still present at the end of the observation period. Because a smaller dose of bupivacaine resulted in a lower level of spinal block, it might be speculated that such a smaller dose results in a lesser degree and shorter duration of sympathovagal imbalance, together with a smaller incidence of severe bradycardia. However, in a prospective study of risk factors for severe bradycardia during spinal anaesthesia,[4] peak block height had a very weak correlation with occurrence of severe bradycardia and no correlation with the magnitude of bradycardia. Sympathovagal imbalance apparently only seems to have a weak correlation with peak block height. From our and previous studies, we also do not know the duration of sympathovagal imbalance in association with spinal anaesthesia.

In summary, patients in the Trendelenburg position had a high incidence of severe bradycardia. We suggest that this position should not be used during recovery from spinal anaesthesia. Severe bradycardia occurring later than 90 min after admission to the PACU was observed in patients who had bradycardia treated successfully in the first 90 min and in patients who had not had severe bradycardia before. This observation is particularly important, as in normal clinical practice some of these patients would have been discharged from the PACU before the occurrence of the first or a subsequent episode of severe bradycardia. Only patients in the hammock position did not have severe bradycardia in this late phase of recovery from spinal anaesthesia. Although the difference in the incidence of severe bradycardia between the hammock and horizontal groups was not significant, in comparison with the Trendelenburg group, only patients in the hammock group had a significantly lower incidence of severe bradycardia occurring later than 90 min after admission to the PACU. Therefore, the hammock position can be considered to be the optimal position for recovery from spinal anaesthesia, especially after discharge from the PACU.

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References

1. Ward R, Bonica J, Freund F, Akamatsu T. Epidural and subarachnoid anesthesia: cardiovascular and respiratory effects. *Journal of the American Medical Association* 1965; **191**: 275–281.
2. Tarkkila P, Kaukinen S. Complications during spinal anesthesia: a prospective study. *Regional Anesthesia* 1991; **16**: 101–106.
3. Tarkkila P, Isola J. A regression model for identifying patients at risk of hypotension, bradycardia, and nausea during spinal anaesthesia. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 554–558.
4. Carpenter R, Caplan R, Brown D, Stephensen C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. *Anesthesiology* 1992; **76**: 906–916.
5. Caplan R, Ward R, Posner K, Cheney F. Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. *Anesthesiology* 1988; **68**: 5–11.
6. Bridenbaugh P, Greene N. Spinal (subarachnoid) neural blockade. In: Cousins MJ, ed. *Neural Blockade in Clinical Anesthesia and Management of Pain.* Philadelphia: JB Lippincott, 1988; 231.
7. Pricolo VE, Burchard KW, Singh AK, Moran JM, Gann DS. Trendelenburg versus PASG application—hemodynamic response in man. *Journal of Trauma* 1986; **26**: 718–726.
8. Greene NM. *Physiology of Spinal Anesthesia.* Baltimore: Williams and Wilkins, 1991.
9. Otton PE, Wilson EJ. The cardiovascular effects of upper thoracic epidural analgesia. *Canadian Anaesthetists Society Journal* 1966; **13**: 541–549.
10. Chamberlain DP, Chamberlain BD. Changes in skin temperature of the trunk and their relationship to sympathetic blockade during spinal anesthesia. *Anesthesiology* 1986; **65**: 139–143.
11. Kawamoto M, Tanaka N, Takasaki M. Power spectral analysis of heart rate variability after spinal anaesthesia. *British Journal of Anaesthesia* 1993; **71**: 523–527.
12. Introna R, Yodlowski E, Pruett J, Montano N, Porta A, Crumrine R. Sympathovagal effects of spinal anesthesia assessed by heart rate variability analysis. *Anesthesia and Analgesia* 1995; **80**: 315–321.
13. Malliani A, Pagani M, Lombardi F. Cardiovascular regulation explored in the frequency domain. *Circulation* 1991; **84**: 482–492.
14. Loffelholz K, Muscholl E. Inhibition by parasympathetic nerve stimulation of the release of noradrenegic transmitter. *Naunyn Schmiedebergs Archives of Pharmacology* 1970; **267**: 181–189.
15. Kolman B, Verrier R, Lown B. The effect of vagus stimulation upon vulnerability of the canine ventricle: role of sympathetic–parasympathetic interactions. *Circulation* 1975; **52**: 578–585.
16. Wilkins R, Bradley S, Friedland C. The acute circulatory effects of the head down position (negative G) in normal man, with a note on some measures designed to relieve cranial congestion in this position. *Journal of Clinical Investigation* 1950; **29**: 940–949.
17. McHugh G, Robinson B. Leg elevation compared with Trendelenburg position: effects on autonomic cardiac control. *British Journal of Anaesthesia* 1994; **73**. 836–837.

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Balanced pre-emptive analgesia: does it work? A double-blind, controlled study in bilaterally symmetrical oral surgery

W. I. CAMPBELL, R. W. KENDRICK AND J. P. H. FEE

Summary

We studied 32 patients undergoing bilateral symmetrical lower third molar surgery under general anaesthesia to determine if the combined effects of pre-emptive local anaesthetic block using 0.5% bupivacaine, together with i.v. tenoxicam and alfentanil had any benefits over postoperative administration. Patients acted as their own controls and were allocated randomly to have surgery start on one side, the second side always being the pre-emptive side. Difference in pain intensity between the two sides was determined using visual analogue scales completed by each individual at 6 h, and at 1, 3 and 6 days after operation. A long-form McGill pain questionnaire was also used to assess difference in pain intensity between the two sides on the morning after surgery. There was no significant difference in pain intensity at any time after surgery. Our findings indicate that the combined use of pre-emptive analgesia from 0.5% bupivacaine, tenoxicam and alfentanil did not reduce postoperative pain intensity in patients undergoing molar exodontia. (*Br. J. Anaesth.* 1998; **81**: 727–730).

Keywords: analgesia, pre-emptive; non-steroidal anti-inflammatory drugs; anaesthetics local, bupivacaine; analgesics opioid, alfentanil; pain, postoperative; surgery, dental

Postoperative pain may be controlled by the use of local anaesthetic block, opioids, non-steroidal anti-inflammatory drugs or a combination of these.[1] It has been proposed that by administering analgesia before nociception, it may be possible to prevent central sensitization.[2] Animal work, together with clinical observations in acute and chronic pain states, appear to confirm this hypothesis.[3–6]

Initially, the results of controlled clinical studies appeared to favour the theory that pre-emptive analgesia was of value in clinical practice.[7–9] Other studies have not shown any benefit of administration of analgesia in a pre-emptive manner.[10–12] Previous studies by us have not illustrated a pre-emptive analgesic effect with the use of local anaesthesia, despite relatively large numbers of subjects either acting as their own controls or in two separate groups.[13 14] The pre-emptive use of a non-steroidal anti-inflammatory drug before surgery may be more beneficial than its action starting after surgical incision.[15] In addition, opioids have been shown to have a beneficial effect if given before rather than after surgical incision.[16–18]

In this study, we determined if there was any benefit in using pre-emptive balanced analgesia. To do this, a bilateral symmetrical surgical model was used to allow patients to act as their own controls and minimize confounding factors, thus increasing the power of the study. Each patient received a non-steroidal anti-inflammatory drug, local anaesthetic block and opioids before incision on one side, and after surgery on the other side.

Patients and methods

The study was approved by the local Ethics Committee. We studied 32 ASA I and II patients, aged 18 yr or more, undergoing removal of both lower third molar teeth, provided that the teeth were bilaterally symmetrical on radiological examination. If upper third molars were to be removed, patients were included only if all four third molars were removed. Patients who gave a history of asthma or aspirin intolerance were excluded. Informed written consent was obtained in each case.

Before surgery, patients were shown how to complete a pain questionnaire, which they retained and completed after surgery. Pain assessment was carried out using two 10-cm vertical visual analogue scales (VAS), one for each operation side, at each of the following times: 6 h after surgery, and on the mornings of days 1, 3 and 6 after surgery. Anchor points were 0=no pain, 100=worst pain possible. A long-form McGill pain questionnaire was also completed on the morning after surgery. Patients were asked to complete the VAS on the left side of the page for their left-sided pain and the VAS on the right side of the page for their right-sided pain. They then completed a single McGill pain questionnaire by placing the letters L (left), R (right) or R+L (both sides) beside the words which described the sensation which they experienced on the morning after surgery. All pain questionnaires were completed independently by the patients and posted back to the author.

The procedure was carried out under general anaesthesia. Anaesthesia was induced with propofol and maintenance with 1.5% halothane and 60%

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nitrous oxide in oxygen via a nasal tracheal tube. Restricted randomization was used to allocate patients to one of two groups. Two bundles of 16 small cards detailing which side to start the operation on were placed in sealed envelopes, shuffled and numbered sequentially. Immediately after induction of anaesthesia, the surgeon opened one of the randomization envelopes. Group A received an inferior alveolar and a long buccal nerve block, using 0.5% plain bupivacaine 2 ml at each nerve, on the left side only. If the upper third molars were also to be removed, buccal infiltration with 0.5% plain bupivacaine 1 ml was administered on the left side. Surgery then commenced on the right (contralateral) side and when this was complete local anaesthetic was injected as above on this side.

Immediately after removal of the first lower tooth, but before wound closure, the surgeon indicated that he was going to operate on the opposite side. Tenoxicam 20 mg, alfentanil 2 mg, atropine 0.3 mg and ondansetron 8 mg were then administered i.v. If heart rate was less than 50 beat min^{-1} further doses of atropine were administered in 0.3 mg increments. Spontaneous respiration was permitted until alfentanil was given when mechanically assisted ventilation was used until the end of operation. Normocapnia was maintained during assisted ventilation. Those patients allocated to group B were treated in an identical manner to those in group A but the sides treated with local anaesthetic before or after surgery were reversed. Ondansetron was administered to prevent nausea.

The purpose of the above procedure was to establish two groups, each of 16 patients: one with surgery commencing on the right and the other with surgery starting on the left. Regardless of grouping, the first side operated on was always the side which was blocked by local anaesthetic after *exodontia*. Surgery did not start on the second side until at least 10 min had elapsed after neuronal block with bupivacaine and at least 5 min before pretreatment with alfentanil and tenoxicam. The anaesthetist and patient were both unaware of the pretreatment sides. If surgery was more difficult on one side or the patient was not bilaterally numb and pain free, they were excluded and their randomization envelope reallocated to the next available patient who met the entry criteria for the study. Surgical difficulty was rated by the surgeon after operation as: (i) simple tooth elevation; (ii) bone removal or tooth division; (iii) bone removal and tooth division; or (iv) as (iii) but very difficult. Analgesia was available after operation as co-codamol (codeine 8 mg and paracetamol 500 mg), two tablets every 4 h, as required.

Difference in pain between the two sides in each patient, as assessed by VAS and McGill pain questionnaires, was analysed using the Wilcoxon matched pairs signed ranks test. The Mann–Whitney *U* test was used to determine if there was a significant difference in pain between the first and second side operated on. Kruskal–Wallis one-way analysis of variance was used to detect differences in pain caused by surgical difficulty. The results of similar research by us indicated that at least 30 subjects would be needed to detect a difference in pain of 10 mm in VAS at 24 h between the two sides in each patient and achieve a power of 90% at the 5% level of significance.[13]

Table 1 Median (interquartile range (IQR)) pain scores of 32 patients after lower third molar extraction under general anaesthesia. The second side operated on was always the pre-emptive side, regardless of grouping

Pain after surgery		Median (IQR)
Visual analogue scale rating (0–100 mm)		
First side	6 h	11 (1, 23)
Second side	6 h	9 (2, 38)
First side	1 day	8 (4, 28)
Second side	1 day	9 (3, 30)
First side	3 days	7 (2, 33)
Second side	3 days	7 (1, 29)
First side	6 days	4 (1, 12)
Second side	6 days	4 (1, 13)
McGill pain questionnaire scores		
First side	1 day	4 (1, 8)
Second side	1 day	4 (2, 8)

Table 2 Difference in pain ratings between the first and second side operated on in patients (n=32) undergoing bilateral symmetrical lower third molar extraction under general anaesthesia (median (interquartile range (IQR)). No significant differences

Differences in pain intensity (second–first side)		Median (IQR)
Visual analogue scale differences at	6 h	0 (-1, 4)
	1 day	1 (0, 5)
	3 days	0 (-1, 2)
	6 days	0 (-1, 4)
McGill pain questionnaire differences at 1 day		0 (0, 1)

Results

We studied 24 women and eight men, but one woman was excluded from group B as one side was not numb after operation. That randomization envelope was used on the next case meeting the entry criteria for the study.

Mean age was 25 (range 18–44) yr. Mean weight was 66 (SD 10.3) kg. The number of patients within each difficulty of surgery grading (rated i–iv) was 6, 10, 12 and 4, respectively. Pain scores for each side are given in table 1 but it was the difference in pain between the two sides of each individual that was used for statistical purposes. Pain intensity did not correlate with difficulty of surgery on the first side operated on. All data were therefore pooled and the difference in pain between the first and second sides operated on in each patient was used to establish if there was an overall meaningful difference in pain intensity (table 2). There was no significant difference in pain at any time between the two sides.

Discussion

Administration of opioids before nociception has been shown to prevent central sensitization but the dose of opioid used must be sufficient to completely block the release of the excitatory amino acids involved in initiating sensitization.[19] Despite this, the apparent value of pre-emptive opioid use does not improve by increasing the dose in excess of the therapeutic norm.[17] In our study, the potent opioid alfentanil was used in a sufficiently large dose to slow heart rate and stop respiration in all patients, until shortly after surgery was complete. Some researchers have illustrated the benefits of pre-emptive opioids in clinical situations.[9,17,18] However, others have been unable to substantiate such a hypothesis.[20,21] Alfentanil was chosen as the opioid for this study because of its rapid onset and short duration.[22]

A non-steroidal anti-inflammatory drug was also used in this study as it is known to prevent peripheral sensitization.[23,24] Its use may be beneficial if administered before rather than after tissue injury.[15] This class of drug is known to have central analgesic properties.[25,26] Tenoxicam was used as it can be given i.v. and it has been shown that analgesia occurs very rapidly even after i.m. use. In a study by Rice and colleagues, comparison of i.m. morphine and ketorolac was made.[27] There was a 25% reduction in pain within 7–8 min after either drug and a 50% reduction in pain after another 25 min. As higher plasma concentrations would be achieved more rapidly after i.v. administration, the speed of analgesic onset would be expected to be more rapid than that after i.m. administration of non-steroidal anti-inflammatory drugs.

The difference in pain scores between the two sides was not significant at any time after surgery. However, all patients had complete analgesia from neuronal block for the first few hours after surgery. Neither the local anaesthetic nor tenoxicam would have had any new clinical effect by 24 h after surgery.[28,29] In particular, the dose of alfentanil used would not have any clinical effect several hours after surgery because of its short half-life.[22,30] Therefore these drugs would not be expected to interfere with pain assessments carried out in the days after surgery, as their therapeutic actions would have ceased on both sides.

It could be argued that the model of bilateral symmetrical surgery is not sound, yet this type of model is used widely by basic scientists, providing much of our physiological knowledge on pain.[3,31] However, the unilateral biochemical changes which have been identified within the spinal cord after ipsilateral limb injury gradually become bilateral over days to weeks in animals.[31–33] The biochemical changes which eventually involve the contralateral side of the spinal cord together with diminishing pain magnitude in the days after surgery may explain the difficulty in identifying any late benefits of pre-emptive analgesia.

The results of this study were disappointing. At no time was there any benefit of pre-emptive analgesia compared with postoperative use, despite administration of analgesics working at three different sites concurrently. Attempts to reduce postoperative pain by pre-emptive techniques using conventional analgesics and techniques are probably unrealistic. Analgesia probably has to be extended well into the healing period to be beneficial but how do we determine that there is an advantage in administering analgesics before rather than after surgery starts, when pain intensity is likely to be very low with both techniques?

References

1. Dahl JB, Rosenberg J, Dirkes WE, Mogensen T, Kehlet H. Prevention of postoperative pain by balanced analgesia. *British Journal of Anaesthesia* 1990; **64**: 518–520.
2. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
3. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature (London)* 1983; **306**: 686–688.
4. Dickenson AH, Sullivan AF. Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. *Pain* 1987; **30**: 349–360.
5. McQuay HJ, Carroll D, Moore RA. Postoperative orthopaedic pain—the effect of opiate premedication and local anaesthetic blocks. *Pain* 1988; **33**: 291–295.
6. Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade *Pain* 1988; 33: 297–301.
7. Jebeles JA, Reilly JS, Gutierrez JF, Bradley EL, Kissin I. The effect of pre-incisional infiltration of tonsils with bupivacaine on the pain following tonsillectomy under general anaesthetic. *Pain* 1991; **47**: 305–308.
8. Ejlersen E, Andersen HB, Eliasen K, Mogensen T. A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. *Anesthesia and Analgesia* 1992; **74**: 495–498.
9. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, Shaw MF. Pre-emptive analgesia: clinical evidence of neuroplasticity contributing to postoperative pain. *Anesthesiology* 1992; **77**: 439–446.
10. Pryle BJ, Vanner RG, Enriquez N, Reynolds F Can pre-emptive lumbar epidural blockade reduce postoperative pain following lower abdominal surgery? *Anaesthesia* 1993; **48**: 120–123.
11. Dierking GW, Dahl JB, Kanstrup J, Dahl A, Kehlet H. Effect of pre- vs postoperative inguinal field block on postoperative pain after herniorrhaphy. *British Journal of Anaesthesia* 1992; **68**: 344 -348.
12. Harrison CA, Morris S, Harvey JS. Effect of ilioinguinal and iliohypogastric nerve block and wound infiltration with 0.5% bupivacaine on postoperative pain after hernia repair. *British Journal of Anaesthesia* 1994; **72**: 691–693.
13. Campbell WI, Kendrick RW. Pre-emptive analgesia using local anaesthesia: a study in bilaterally symmetrical surgery. *British Journal of Anaesthesia* 1997; **79**: 657–659.
14. Campbell WI, Kendrick RW, Ramsay-Baggs P, McCaughey W. The effect of preoperative administration of bupivacaine compared with its postoperative use. *Anaesthesia* 1997; **52**: 1212–1216.
15. Campbell WI, Kendrick R, Patterson C. Intravenous diclofenac sodium. Does its administration before operation suppress postoperative pain? *Anaesthesia* 1990; **45**: 763–766.
16. Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. *Lancet* 1993; **342**: 73–75.
17. Collis R, Brandner B, Bromley LM, Woolf CJ. Is there any clinical advantage of increasing the pre-emptive dose of morphine or combining pre-incisional with postoperative morphine administration? *British Journal of Anaesthesia* 1995; **74**: 396–399.
18. Yoon DM, Ahn EY, Lee YW. Effect of pre-emptive analgesia with intravenous morphine for postoperative pain relief. *8th World Congress on Pain. International Association for the Study of Pain.* Seattle: IASP Press, 1996; 46–47.
19. Dickenson AH. A cure for wind-up: NMDA receptor antagonists as potential analgesics. *Trends in Pharmacological Sciences* 1990; **11**: 307–309.
20. Wilson RJT, Leith S, Jackson IJB, Hunter D. Pre-emptive analgesia from intravenous administration of opioids. No effect with alfentanil. *Anaesthesia* 1994; **49**: 591–593.
21. Mansfield M, Meikle R, Miller C. A trial of pre-emptive analgesia: Influence of timing of preoperative alfentanil on postoperative pain and analgesic requirements. *Anaesthesia* 1994, **49**: 1091–1093.
22. Tverskoy M, Oren M, Dashkovsky I, Kissin I. Alfentanil dose–response relationships for relief of postoperative pain. *Anesthesia and Analgesia* 1996; **83**: 387–393.
23. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biology* 1971; **231**: 232–235.
24. Ferreira SH, Moncada S, Vane JR. Prostaglandins and the mechanism of analgesia produced by aspirin-like drugs. *British Journal of Pharmacology* 1973; **49**: 86–97.
25. Malmberg AB, Yaksh TL. Antinociceptive actions of spinal nonsteroidal antiinflammatory agents on the formalin test in the rat. *Journal of Pharmacology and Experimental Therapeutics* 1992; **263**: 136–146.
26. Wang BC, Li D, Hiller JM, Hillman DE, Pasterack BS, Turndorf H. The antinociceptive effect of S-(+)-ibuprofen in rabbits: epidural versus intravenous administration. *Anesthesia and Analgesia* 1995; **80**: 92–96

27. Rice ASC, Lloyd J, Miller CG, Bullingham RE, O'Sullivan GM. A double-blind study of the speed of onset of analgesia following intramuscular administration of ketorolac tromethamine in comparison to intramuscular morphine and placebo. *Anaesthesia* 1991; **46**: 541–544.
28. Knudsen KE, Brofeldt S, Mikkelsen S, Bille M, Brennum J, Dahl JB. Peritonsillar infiltration with low-dose tenoxicam after tonsillectomy. *British Journal of Anaesthesia* 1995; **75**: 286–288.
29. Elhakim M, Nafie M. I.v. tenoxicam for analgesia during Caesarean section. *British Journal of Anaesthesia* 1995; **74**: 643–646
30. Irwin MG, Jones RDM, Visram AR, Kenny GNC. Patient-controlled alfentanil. Target-controlled infusion for postoperative analgesia. *Anaesthesia* 1996; **51**: 427–430.
31. Mao J, Price DD, Coghill RC, Mayer DJ, Hayes RL. Spatial patterns of spinal cord [14C]-2-deoxyglucose metabolic activity in a rat model of painful peripheral mononeuropathy. *Pain* 1992; **50**: 89–100.
32. Woolf CJ. Long term alterations in the excitability of the flexion reflex produced by peripheral tissue injury in the chronic decerebrate rat. *Pain* 1984; **18**: 325–343.
33. Stevens CW, Kajander KC, Bennett GJ, Seybold VS. Bilateral and differential changes in spinal mu, delta and kappa opioid binding in painful, unilateral neuropathy. *Pain* 1991; **46**: 315–326.

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Dextromethorphan and pain after total abdominal hysterectomy

P. M. McConaghy, P. McSorley, W. McCaughey and W. I. Campbell

Summary

Dextromethorphan is an *N*-methyl-D-aspartate (NMDA) receptor antagonist which has been shown to inhibit the development of cutaneous secondary hyperalgesia after tissue trauma. We studied 60 ASA I–II patients undergoing total abdominal hysterectomy in a randomized, double-blind, placebo-controlled study. Patients received either dextromethorphan 27 mg capsules, two doses before operation and three doses in the first 24 h after operation, or placebo. Visual analogue pain scores (VAS) at 24 and 48 h were assessed at rest, on coughing and on sitting up, and were not significantly different between groups. Morphine consumption from a patient-controlled analgesia (PCA) device was also not significantly different between groups. Evidence of secondary hyperalgesia was assessed with von Frey hairs 10 cm above the Pfannenstiel incision. Both groups of patients exhibited evidence of secondary hyperalgesia after 24 and 48 h but there were no significant differences between groups. There was also no difference between groups in VAS scores at 1 month. (*Br. J. Anaesth.* 1998; **81**: 731–736).

Keywords: pharmacology, dextromethorphan; pain, postoperative; pain, mechanism.

Secondary hyperalgesia is a pain state which may develop during and after surgery and is manifest clinically as mechanical allodynia, that is the perception of pain in response to normally innocuous mechanical stimuli, in normal tissue surrounding an area of tissue trauma.[1] The development of this pain state has been shown previously to be dependent on activation of the *N*-methyl-D-aspartate (NMDA) receptor located at the dorsal horn of the spinal cord.[2-5] Secondary hyperalgesia has been shown to contribute to generation of pain after tissue injury in animals.[2 6 7] Richmond, Bromley and Woolf [8] have shown, in humans, that postoperative morphine consumption after total abdominal hysterectomy is decreased when an attempt is made to prevent perioperative activation of the NMDA receptor by pre-emptive administration of i.v. morphine.

Dextromethorphan is a weak, non-competitive NMDA antagonist which has been used as an antitussive agent for more than 30 yr. It has been shown to inhibit the development of cutaneous secondary hyperalgeisa in humans after peripheral burn injury[9 10] and to reduce temporal summation of pain which is an NMDA-dependent event.[11]

The aims of this study were to assess the analgesic benefits of the NMDA antagonist, dextromethorphan, in patients undergoing total abdominal hysterectomy, when the drug was administered in the perioperative period.

Patients and methods

The study was approved by the Queen's University Research Ethics Committee. Patients presenting for elective total abdominal hysterectomy with or without bilateral sapingo-oophorectomy were recruited after providing written, informed consent, and were allocated randomly (computer-generated list) to either the active or control group. Exclusion criteria for entry to the study included history of a chronic pain syndrome (e.g. fibromyalgia), patients receiving drugs with actions at the spinal cord (e.g. antidepressants), or aspirin within 2 weeks of admission. The consumption of non-steroidal anti-inflammatory drugs (NSAID) other than aspirin was discontinued at least 24 h before operation.

A 100-mm visual analogue score (VAS) for pain was explained to the patients at the preoperative assessment (0=no pain and 100=worst imaginable pain). It was explained how their wounds would be assessed after operation with von Frey hairs, which are a series of 20 nylon monofilaments that exert a specific force when bent end on to the patient's skin.

All patients received diazepam 10 mg on the evening before surgery, and diazepam 10 mg, 1–2 h before operation. Patients in the active treatment group also received dextromethorphan 27 mg capsules before operation: one on the night before surgery and one with their premedicant. After operation three further doses were given at 8, 16 and 24 h after operation. Patients in the control group received placebo capsules at the same time intervals. All of the study drugs were prepared by the hospital pharmacy and the study was carried out in a double-blind manner.

On arrival in the operating theatre, an i.v. cannula was inserted into the dorsum of the hand and 1 litre of Hartmann's solution was commenced. Monitors connected before induction of anaesthesia included peripheral oxygen saturation (Sp_{O_2}), electrocardiograph (ECG) and arterial pressure (AP) recorded

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Table 1 Patients excluded from the study within the first 24 h

Group	Reason for exclusion
Placebo	Received diclofenac
Placebo	Received diclofenac
Placebo	Returned to operating theatre
Placebo	Returned to operating theatre
Active	Received diclofenac
Active	Received i.m. morphine after operation
Active	Vaginal hysterectomy

Table 2 Patient data (mean (SD or range)). No significant differences

	Dextromethorphan (*n*=27)	Placebo (*n*=26)
Age (yr)	45 (30–58)	45 (37–63)
Weight (kg)	65 (11.5)	66 (12.1)
Height (cm)	156 (23.6)	162 (5.0)
Duration of surgery (min)	56 (18.8)	63 (13 7)
Intraoperative morphine (mg)	7 (1 4)	7 (1.4)

non-invasively at 5-min intervals. Each patient was preoxygenated for 2 min with 100% oxygen, after which anaesthesia was induced with propofol 2–3 mg kg^{-1}. Tracheal intubation was facilitated with atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained with 1–3% isoflurane and 30–40% oxygen in nitrous oxide, and the patients' lungs were ventilated to normocapnia. Ten minutes after a standardized Pfannenstiel incision was made, morphine 0.1–0.15 mg kg^{-1} i.v. was given, with further increments administered at the discretion of the attending anaesthetist. Other drugs given during the intraoperative period were: antibiotics (either amoxycillin–clavulonic acid 1.2 g or cefuroxime 1.5 g), ondansetron 4 mg, neostigmine 2.5 mg and glycopyrrolate 0.5 mg.

After tracheal extubation at the end of operation, patients were transferred to the recovery ward where the nursing staff were free to administer bolus doses of morphine 2 mg i.v. every 3 min as required. Patients were assessed by an anaesthetist if they received morphine 10 mg before additional doses were prescribed. I.v. morphine was also available via a patient-controlled analgesia (PCA) system set to deliver 1-mg boluses of morphine with a 5-min lockout interval. Postoperative nausea and vomiting were treated with prochlorperazine 12.5 mg i.m. 8 h as required. No NSAID was prescribed for the first 48 h after operation.

Patients were assessed after 24 and 48 h by one of the authors. Total postoperative morphine consumption, including that received in the recovery ward, was recorded. VAS pain scores with the patient lying at rest, on coughing (maximal cough after vital capacity inspiratory breath) and on sitting up from the lying position were recorded also.

Touch thresholds were determined at the medial side of the patient's right forearm and 10 cm above the incision, with von Frey hairs. Three points were examined above the wound: one at the midline and one halfway between the midline and the edge of the wound on the left and right sides. Patients were asked to close their eyes and von Frey hair No. 1 was applied to the area to be tested. Each hair was applied once to the site, and the patient was asked to report when they were first aware of the light touch of the hair, which was recorded as the touch threshold. Pain thresholds were determined at the same sites as the touch thresholds. Patients were asked to open their eyes for this assessment and to report when the sensation elicited by the von Frey hair first became painful. This force was recorded as the pain threshold. The threshold at the wound for touch and pain was subtracted from that at the forearm to yield a "von Frey threshold" for each assessment.[8]

All patients were given a written questionnaire for completion 1 month after operation. They were asked if they still had pain around their wound and if they had, their worst daily VAS pain score. If they had no pain, duration of postoperative wound pain was elicited. They were asked also if they still required analgesics for wound pain, and if so, which analgesics they were taking.

Statistical analysis was carried out using SPSS for Windows Version 7 operated from a 133 MHz IBM compatible PC. Patient data, VAS scores, morphine consumption and von Frey thresholds were analysed with the Mann–Whitney *U* test. Duration of postoperative pain and VAS scores at 1 month were also compared with the Mann–Whitney test. The incidence of side effects was compared using the chi-square test. A significant result was assumed at $P<0.05$.

The study was able to determine, with 90% power at the 5% significance level, a difference of at least 14 mm in VAS scores at rest and on sitting up, at 24 h, and 19 mm on coughing at 24 h. A difference in 24-h morphine consumption of 18 mg between groups could be detected at the same level of power and significance.

Results

Sixty patients were recruited to the study although seven patients were excluded within the first 24 h (table 1). Data from 53 patients were available for analysis, 27 from the active treatment group and 26 from the placebo group. There were no significant differences between groups for age, weight, height, duration of surgery or intraoperative morphine consumption (table 2).

Total postoperative morphine consumption was similar between groups after 24 h (fig. 1) and there were no significant differences between VAS pain scores at rest, on coughing or on sitting up (fig. 2).

Within the first few weeks of the study commencing, the nurses on the gynaecology ward expressed their concern that patients in the study were being disadvantaged for several reasons. First, they had to continue receiving PCA morphine while those not in the study had their PCA devices removed after 24 h to facilitate mobilization. Second, they were prevented from receiving diclofenac on the second postoperative day, again contrary to standard treatment for this group of patients in this particular hospital.

After hearing these views, we felt that if there was any doubt that these patients were disadvantaged through involvement in the study, that the protocol should be altered. Thus it was decided to omit the 48-h assessment and to prescribe diclofenac after the 24-h assessment, where appropriate. However, assessments at 48 h for 26 patients were obtained before this decision was made.

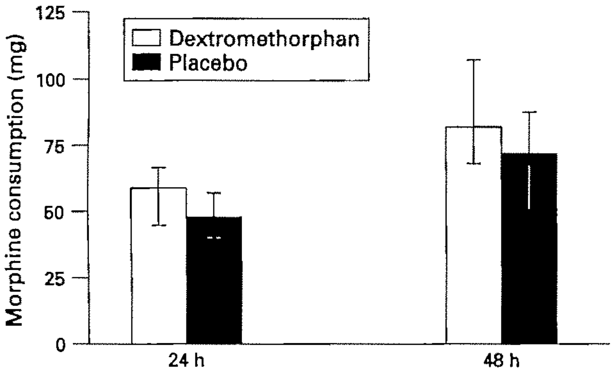

Figure 1 Postoperative morphine consumption (median, interquartile range) at 24 h (n=27 in the dextromethorphan group and n=26 in the placebo group) and at 48 h (n=14 in the dextromethorphan group and n=12 in the placebo group) No significant differences

The von Frey thresholds between groups for pain were not significantly different, with both showing evidence of mechanical allodynia in the areas tested, while the thresholds for touch were also comparable, with the slightly negative values indicating some decreased sensitivity to light touch in the area of allodynia (table 3). At 48 h, the results from 27 patients were available for analysis, 15 from the active treatment group. However, one patient from the active treatment group was unable to co-operate with VAS measurements because of nausea, although she was able to complete the other parts of the assessment.

Morphine consumption was comparable after 48 h (fig. 1) while there were no significant differences in VAS scores at rest, on coughing or on sitting up (fig. 3). The von Frey thresholds for pain were also comparable between groups, although a significant difference was found in touch thresholds (table 3).

The incidence of side effects, possibly attributable to dextromethorphan, is shown in table 4. Compliance with the study drug regimen was 100%, despite the high incidence of postoperative nausea.

Postoperative questionnaires were returned after 1 month by 39 patients, 19 from the active treatment group. There were no significant differences between pain scores (mm) in the dextromethorphan and placebo groups after 1 month (median 0.0 (interquartile range 0–19) *vs* 15.5 (0–23), P=0.21).

Discussion

We have shown that there was no obvious benefit in perioperative administration of dextromethorphan in patients undergoing total abdominal hysterectomy when used within the confines of the chosen anaesthetic regimen, on morphine consumption, early and late postoperative pain or clinical evidence of secondary hyperalgesia.

Table 3 Von Frey thresholds (g) for touch and pain, expressed as median (interquartile range). The threshold for touch in the active treatment group was greater at 48 h

	Dextromethorphan	Placebo	*P*
24 h	(n=27)	(n=26)	
Touch	0 (–0.89–0.00)	1 (–1.78–0.00)	0.20
Pain	60 (0.53–81.3)	79 (12.9–152.9)	0.20
48 h	(n=15)	(n=12)	
Touch	0 (0 to –0.01)	–0.7 (–2 to –0.11)	0.04
Pain	13 (0–38)	2 (0–55)	0.58

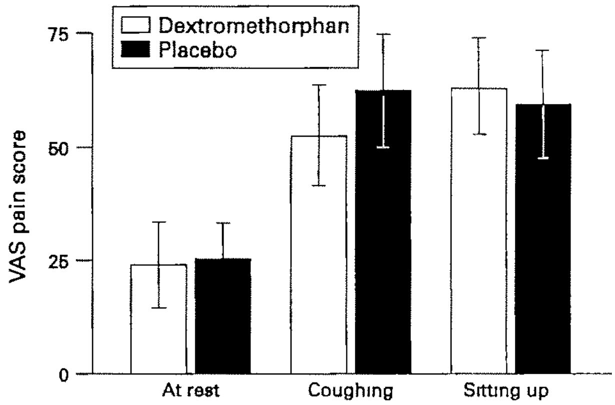

Figure 2 VAS pain scores at 24 h in the dextromethorphan group (n=27) and in the placebo group (n=26), at rest, on coughing and on sitting up from the lying position (median, interquartile range) No significant differences.

Much work in animals has shown that the receptive fields of dorsal horn neurones expand after peripheral inflammation[6] with an increased state of excitability developing centrally which may persist long after afferent C-fibre activity has ceased.[12 13] Clinically, this is manifest as mechanical allodynia at peripheral sites distant from the inflamed area, and hyperpathia (i.e. increased pain in response to a normally painful stimulus). Our patients, on both the first and second postoperative days, displayed evidence of secondary hyperalgesia with mechanical allodynia 10 cm above the skin incision, as manifest by positive von Frey thresholds. We did not examine evidence of hyperpathia, as this would have involved application of a painful force to the area of allodynia and patients being asked to record the VAS to this force. We felt that patient compliance with this part of the study would have been low in view of the fact that a detailed and time-consuming assessment was already being carried out. However, previous workers have also omitted this assessment in their measurement of secondary hyperalgesia after total abdominal hysterectomy[8 14] and have relied instead on von Frey pain thresholds to assess methods of inhibiting dorsal horn changes.

Dextromethorphan is a water-soluble agent with weak, non-competitive NMDA blocking properties.[15 16] It is metabolized by O-dealkylation to yield the active metabolite dextrorphan, which is a more potent antagonist at the NMDA receptor.[16 17] The efficacy of the NMDA-blocking properties of

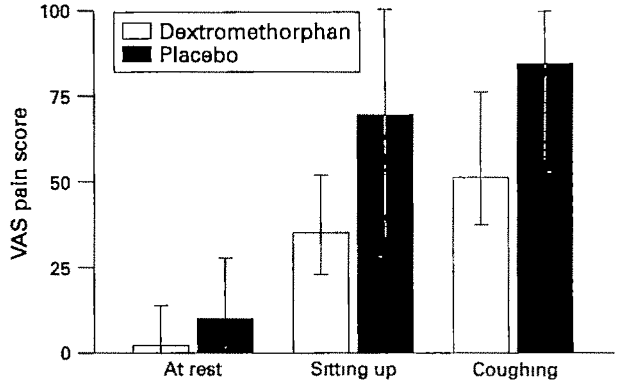

Figure 3 VAS pain scores at 48 h in the dextromethorphan and placebo groups, at rest, on coughing and on sitting up from the lying position (median, interquartile range) No significant differences.

Table 4 Incidence of side effects attributable to dextromethorphan after 24 and 48 h (number of patients affected (%)). No significant differences

	Dextromethorphan	Placebo
0–24 h	(*n*=27)	(*n*=26)
Dizziness	12 (44)	11 (42)
Hot flushes	7 (26)	4 (15)
Tremor	5 (19)	6 (23)
Constipation	20 (74)	24 (92)
Drowsiness	24 (89)	26 (100)
Heartburn	6 (22)	26 (100)
Nausea	19 (70)	19 (73)
Vomiting	8 (30)	14 (54)
24–48 h	(*n*=14)	(*n*=12)
Dizziness	6 (43)	5 (42)
Hot flushes	4 (29)	5 (38)
Tremor	0 (0)	6 (50)
Constipation	11 (79)	5 (42)
Heartburn	5 (36)	3 (25)
Nausea	5 (36)	3 (25)
Vomiting	2 (14)	1 (8)

dextromethorphan have been shown in several animal studies, where it afforded neuronal protection in an ischaemic brain model,[18,19] inhibited the development of tolerance to morphine[20,21] and was neuroprotective in glutamate-induced neuronal injury.[22] Electrophysiological work has also shown that dextromethorphan produced a reduction in wind-up after repetitive C-fibre stimulation.[23] In human studies, it has also been shown to reduce the clinical evidence of secondary hyperalgesia after thermal injury.[9,11] The active metabolite of dextromethorphan, dextrorphan, has also been shown to be beneficial in animal models where antagonism of the NMDA receptor is the desired outcome, for example in studies of neuropathic pain.[10,24]

Although the above studies provide clinical evidence that dextromethorphan exhibits NMDA-blocking properties, the exact site of action remains unresolved. It seems to possess both presynaptic actions, where it inhibits the release of glutamate at the dorsal horn,[25] together with postsynaptic actions. However, its site of postsynaptic action is not certain as it possesses relatively low affinity for phencyclidine binding sites and has little affinity for MK-801 or glycine recognition sites. Thus indirect modulation of the NMDA receptor may be the mechanism by which its postsynaptic actions are mediated.[22] In contrast, dextrorphan exerts its effects via binding to the phencyclidine site on the NMDA receptor complex.

Work has also been carried out which has produced negative results. Kauppila, Gronroos and Pertovaara,[26] in a study in volunteers, found that dextromethorphan 100 mg orally did not alter visual analogue pain scores after experimental limb ischaemia or topical capsaicin injection. When a dose of 200 mg was given, the incidence of side effects was 100% with withdrawal of 50% of the volunteers from the study. McQuay and colleagues[27] investigated dextromethorphan in patients with neuropathic pain at doses of 40.5 mg and 81 mg daily. No significant analgesic benefit was shown, while seven of 19 patients in the study withdrew because of adverse effects.

Dextromethorphan has been available as an antitussive agent for more than 30 yr and has a strong safety profile with few severe drug reactions.[28–30] However, troublesome side effects occur as the dose is increased.[27,31] McQuay and colleagues[27] found that significant side effects were produced with 81 mg daily in patients with neuropathic pain, but the optimum dose for NMDA antagonism in the perioperative period has not been determined. Hollander and colleagues[31] have used up to 10 mg kg^{-1} day^{-1} for patients with amyotrophic lateral sclerosis, while Albers and colleagues[28] found that 60 mg qid was free from side effects in patients at risk of brain ischaemia. In their study on human volunteers, Price and colleagues[11] found that oral doses of 30 mg and 45 mg were effective at reducing the temporal summation of second pain after peripheral thermal injury. The optimum dose of dextromethorphan in the perioperative period is not known, although it is probable that the doses used in this study were too small, as the incidence of adverse effects attributable to dextromethorphan was not significantly different between the two groups. A dose-finding study for dextromethorphan in the perioperative period would enable the maximum acceptable dose to be assessed after surgery. Coderre and Van Empel[32,33] have shown that the antinociceptive effects of NMDA antagonists in persistent nociceptive models (formalin test) were apparent only at doses which produced significant adverse side effects. The antinociceptive effects were reported to be far from maximal despite significant side effects of both competitive and non-competitive NMDA antagonists administered intrathecally. If the same situation applies to humans in the perioperative period, then few NMDA antagonists would be suitable for use in this period because of the poor adverse effect profile at higher doses.

Another interpretation of our results is that NMDA receptor antagonism did occur, but that this was not detectable using mechanical allodynia, and that thermal allodynia should have been examined also. This is supported by evidence from animal studies which has shown that NMDA receptor activation alone generates thermal allodynia and hyperalgesia, while mechanical allodynia and hyperalgesia require activation of AMPA and metabotropic glutamate receptors, the effects of which are enhanced by NMDA receptor activation.[34] However, many previous studies in animals have shown that NMDA receptor activation after peripheral inflammation leads to generation of mechanical allodynia and the intensity of this is diminished when efforts are made to inhibit activation of the NMDA receptor.[3–6,35,36] More recent work, however, has shown that postoperative pain behaviour in a rat model is not improved by administration of an NMDA antagonist intrathecally.[37]

The intraoperative analgesic regimen in theatre involved administration of i.v. morphine 10 min after skin incision. Although this differs from our normal practice, when an opioid is given at induction of anaesthesia before skin incision, we felt that our patients would not be disadvantaged by this study regimen. Previous studies have shown that pre-incisional morphine in this group of patients prevents the development of secondary hyperalgesia in the first 24 h after operation[8,14] and that there is significant evidence of secondary hyperalgesia if morphine administration is left until closure of the peritoneum.[8] Completely obtunding the development of secondary hyperalgesia by giving morphine at induction of anaesthesia would have resulted in the need for large numbers of patients in our study to show a difference between active and placebo groups. Alternatively, leaving morphine administration until the end of operation may have exposed our patients to unnecessary morbidity. It was decided that administration 10 min after skin incision was a reasonable compromise, as preclinical studies suggest that opioids delivered before the end of surgery may have a beneficial effect on the dorsal horn.[38] However, as our results have shown, this resulted in clinical evidence of NMDA receptor activation, although we cannot say how this would compare with groups given morphine before incision or on peritoneal closure. Further work on the optimum timing of administration of intraoperative opioids is required.

It is interesting that the combined use of an agent with presynaptic actions at the dorsal horn (i.e. morphine), together with an agent with postsynaptic actions (i.e. dextromethorphan), did not prevent the development of secondary hyperalgesia, as the combination of these groups of agents produces synergistic effects at the dorsal horn.[39]

In summary, we have shown that the perioperative use of the NMDA antagonist, dextromethorphan, did not offer any benefit to patients undergoing abdominal hysterectomy within the confines of the study methodology.

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References

1. Woolf CJ. Recent advances in the pathophysiolgy of acute pain. *British Journal of Anaesthesia* 1989; **63**: 139–146.
2. Haley JE, Sullivan AF, Dickenson AH. Evidence for spinal N-methyl-D-aspartate receptor involvement in prolonged chemical nociception in the rat. *Brain Research* 1990; **518**: 218–222.
3. Schaible HG, Grubb BD, Neugebauer V, Oppmann M. The activity of NMDA antagonists on neural activity in cat spinal cord evoked by acute inflammation in the knee joint. *European Journal of Neuroscience* 1991; **3**: 981–991.
4. Ren K, Williams GM, Hylden JKL, Ruda MA, Dubner R. The effects of a non-competitive NMDA receptor antagonist, MK-801, on behavioral hyperalgesia and dorsal horn neuronal activity in rats with unilateral inflammation. *Pain* 1992; **50**: 331–344.
5. Warncke T, Stubhaug A, Jorum E. Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1997; **72**: 99–106.
6. Hylden JLK, Nahin RL, Traub RJ, Dubner R. Expansion of receptive fields of spinal lamina I projection neurons in rats with unilateral adjuvant-induced inflammation: the contribution of dorsal horn mechanisms. *Pain* 1989; **37**: 229–243.
7. Woolf CJ, King AE. Dynamic alterations in the cutaneous mechanoreceptive fields of dorsal horn neurons in the rat spinal cord. *Journal of Neuroscience* 1990; **10**: 2717–2726.
8. Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. *Lancet* 1993; **342**: 73–75.
9. Ilkjaer S, Dirks J, Brennum J, Wernberg M, Dahl JB. Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans. *British Journal of Anaesthesia* 1997; **79**: 600–605.
10. Tal M, Bennett GJ Dextromethorphan relieves neuropathic heat-evoked hyperalgesia in the rat. *Neuroscience Letters* 1993; **151**: 107–110.
11. Price DD, Mao J, Frenk H, Mayer DJ. The *N*-methyl-D-aspartate (NMDA) receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* 1994; **59**· 165–174.
12. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature (London)* 1983; **306**: 686–688.
13. Cook AJ, Woolf CJ, Wall PD, McMahon SB Dynamic receptive field plasticity in rat spinal dorsal horn following C-primary afferent input. *Nature (London)* 1987; **325**: 151–153
14. Collis R, Brandner B, Bromley LM, Woolf CJ. Is there any clinical advantage of increasing the pre-emptive dose of morphine or combining pre-incisional with postoperative morphine administration? *British Journal of Anaesthesia* 1995; **74**: 396–399.
15. Wong BY, Coulter DA, Choi DW, Price DA. Dextrorphan and dextromethorphan, common antitussives, are antiepileptic and antagonize *N*-methyl-D-aspartate in brain slices. *Neuroscience Letters* 1988; **85**: 261–266.
16. Church J, Jones MG, Davies SN, Lodge D. Antitussive agents as N-methylaspartate antagonists· further studies. *Canadian Journal of Physiology and Pharmacology* 1989; **67**: 561–567.
17. Church J, Lodge D, Berry SC. Differential effects of dextrorphan and levorphanol on the excitation of rat spinal neurons by amino acids. *European Journal of Pharmacology* 1985; **111**: 185–190.
18. George CP, Goldberg MP, Choi DW, Steinberg GK. Dextromethorphan reduces neocortical ischemic neuronal damage in vivo. *Brain Research* 1988; **440**. 375–379.
19. Bokesh NG, Hudson AL, Price GW. GABA$_A$ and GABA$_B$ receptor site distribution in the rat central nervous system *Neuroscience* 1987; **20**: 365–383.
20. Elliott KJ, Brodsky M, Hyansky AD, Foley KM, Inturrisi CE. Dextromethorphan suppresses both formalin-induced nociceptive behavior and the formalin-induced increase in spinal cord c-fos mRNA. *Pain* 1995; **61**: 401–409.
21. Manning BH, Mao J, Frenk H, Price DD, Mayer DJ. Continuous co-administration of dextromethorphan or MK-801 with morphine attenuation of morphine dependence and naloxone-reversible attenuation of morphine tolerance. *Pain* 1996; **67**: 79–88.
22. Tortella FC, Klette KL, DeCoster MA, Davis BJ, Newman AH. Dextromethorphan analogs are neuroprotective in vitro and block glutamate-induced excitoxic calcium signals in neurons. *Neuroscience Letters* 1995; **198**: 79–82.
23. Dickenson AH, Sullivan AF, Stanfa LC, McQuay HJ. Dextromethorphan and levorphanol on dorsal horn nociceptive neurones in the rat. *Neuropharmacology* 1991; **30**: 1303–1308.
24. Mao J, Price DD, Hayes RL, Lu J, Mayer DJ, Frenk H. Intrathecal treatment with dextrorphan or ketamine potently reduces pain-related behaviors in a rat model of peripheral mononeuropathy. *Brain Research* 1993, **605**· 164–168.
25. Annels SJ, Ellis Y, Davies JA. Non-opioid antitussives inhibit endogenous glutamate release from rabbit hippocampal slices. *Brain Research* 1991; **564**: 341–343
26. Kauppila T, Gronroos M, Pertovaara A. An attempt to attenuate experimental pain in humans by dextromethorphan. *Pharmacology, Biochemistry and Behavior* 1995; **52**: 641–644.
27. McQuay HJ, Carroll D, Jadad AR, Glynn CJ, Jack T, Moore RA, Wiffen PJ. Dextromethorphan for the treatment of neuropathic pain: a double-blind randomised controlled trial with integral n-of-1 design. *Pain* 1994, **59**: 127–133.
28. Albers GW, Saenz RE, Moses JA, Choi DW. Safety and tolerance of oral dextromethorphan in patients at risk for brain ischaemia. *Stroke* 1991; **22**: 1075–1077.
29. Bem JL, Peck R. Dextromethorphan. An overview of safety issues. *Drug Safety* 1992; **3**: 190–199.
30. Steinberg GK, Bell TE, Yenari MA. Dose escalation safety and tolerance of the N-methyl-D-aspartate antagonist dextromethorphan in neurosurgery patients. *Journal of Neurosurgery* 1996; **84**: 860–866.
31. Hollander D, Pradas J, Kaplan R, McLeod HL, Evans WE, Munsat T. High-dose dextromethorphan in amyotrophic lateral sclerosis: phase 1 safety and pharmacokinetic studies. *Annals of Neurology* 1994; **36**: 920–924.
32. Coderre TJ, Van Empel I. The utility of excitatory amino acid (EAA) antagonists as analgesic agents. I Comparison of the antinociceptive activity of various classes of EAA antagonists in mechanical, thermal and chemical nociceptive tests *Pain* 1994; **59**. 345–352
33. Coderre TJ, Van Empel I. The utility of excitatory amino acid (EAA) antagonists as analgesic agents. II. Assessment of the

antinociceptive activity of combinations of competitive and non-competitive NMDA antagonists with agents acting at allosteric-glycine and polyamine receptor sites. *Pain* 1994; **59**: 353–359.

34. Meller ST, Gebhart GF. Spinal mediators of hyperalgesia. *Drugs* 1994; 47 (Suppl. 5): 10–20.
35. Dougherty PM, Willims WD. Enhanced responses of spinothalamic tract neurons to excitatory aminoacids accompany capsaicin induced sensitization in the monkey. *Journal of Neuroscience* 1992; **12**: 883–895.
36. Ren K, Hylden JKL, Williams GM, Ruda MA, Dubner R. The effects of a non-competitive NMDA receptor antagonist, MK-801, on behavioral hyperalgesia and dorsal horn neuronal activity in rats with unilateral inflammation. *Pain* 1992; **50**: 331–344.
37. Zahn PK, Brennan TJ. Lack of effect of intrathecally administered N-methyl-D-aspartate receptor antagonists in a rat model for postoperative pain. *Anesthesiology* 1998; **88**: 143–156.
38. Yaksh TL. The spinal pharmacology of facilitation of afferent processing evoked by high-threshold afferent input of the post injury pain state. *Current Opinion in Neurology and Neurosurgery* 1993; **6**: 250–256.
39. Chapman V, Dickenson AH. The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. *Brain Research* 1992; **573**: 321–323.

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Tramadol or morphine administered during operation: a study of immediate postoperative effects after abdominal hysterectomy

J. F. Coetzee and H. van Loggerenberg

Summary

Tramadol may cause awareness and EEG activation during anaesthesia. We compared tramadol with morphine, administered during wound-closure, surmising that tramadol may cause earlier awakening, more rapid recovery, less respiratory depression and equivalent pain relief. Forty patients received nitrous oxide–enflurane for abdominal surgery. At wound closure, patients received tramadol 3 mg kg^{-1} or morphine 0.2 mg kg^{-1} and end-tidal enflurane concentrations were maintained at 0.5 kPa until skin closure, whereupon anaesthesia was discontinued. Times to spontaneous respiration, awakening and orientation were similar in the two groups, as were blood-gas tensions, ventilatory frequency, pain scores and incidence of nausea. Half of each group required supplementary analgesia during their 90-min stay in the recovery room. P-deletion counts improved more rapidly in the tramadol group. This study confirms previous reports that tramadol did not antagonize the hypnotic effects of volatile anaesthetics. Tramadol, administered during operation, was as effective as morphine in providing postoperative analgesia while permitting more rapid psychomotor recovery. (*Br. J. Anaesth.* 1998; **81**: 737–741).

Keywords: analgesics non-opioid, tramadol; analgesics opioid, morphine; pain, postoperative; analgesia, gynaecological

Tramadol has been shown to increase the incidence of intraoperative awareness during nitrous oxide–oxygen anaesthesia.[1] Coetzee, Maritz and du Toit[2] showed that awareness is unlikely during light, stable anaesthesia with nitrous oxide and isoflurane. However, they demonstrated that tramadol caused dose-dependent activation of the electroencephalogram (EEG). Houmes and colleagues showed tramadol to be as effective and safe as morphine for the treatment of postoperative pain.[3] Potential advantages of administering tramadol for postoperative pain relief include long duration of action[4] and limited respiratory depressant effects.[3,5] Maximum analgesia occurs 1–2 h after i.v. administration, therefore tramadol should preferably be given during operation because administration after inhalation anaesthesia has been shown to provide inadequate postoperative pain relief.[4,6]

In this study, we have compared the effects of tramadol or morphine administered during wound closure. The hypothesis was that tramadol would cause earlier awakening after anaesthesia, more rapid recovery of cognitive function, less respiratory depression during the immediate postoperative period and equivalent pain relief.

Patients and methods:

After obtaining approval from the Institutional Ethics Committee and informed consent, we studied 40 patients, ASA I or II, aged 23–67 yr, weighing 41–100 kg, in a comparative, double-blind, randomized study. Exclusion criteria were cardiac or pulmonary disease, pregnancy, lactation, administration of analgesic or psychotropic drugs, history of central nervous system disease (including epilepsy), history of a disabling psychiatric disorder and allergy to opioids. All patients underwent abdominal hysterectomy via a lower abdominal incision performed by various surgeons.

Postoperative pain intensity and cognitive function were assessed using a visual analogue scale (VAS) and a p-deletion test. In the latter test, the patient was presented with an A4 sheet containing 62 lines of 80 close-spaced, randomly typed, lower case letters per line and requested to delete as many letter p's as possible without omission, reading from left to right down the page.[7,8] All patients met the anaesthetist on the day before surgery who instructed them on how to use the VAS and p-deletion test. A baseline p-deletion score was obtained.

Patients were allocated randomly to one of two groups. Premedication and anaesthetic technique were the same in both groups. Premedication comprised diazepam 10 mg orally, administered 2 h before operation. Anaesthesia was induced with fentanyl 4 μg kg^{-1} followed by propofol 1.5–2.0 mg kg^{-1} and vecuronium 0.08 mg kg^{-1}. The patient's trachea was intubated and ventilation was controlled using a circle-absorber breathing system to maintain end-expired carbon dioxide partial pressure at 4.0–4.5 kPa. Anaesthesia was maintained using enflurane and 60% nitrous oxide in oxygen. Enflurane concentrations were monitored using an infrared anaesthetic gas monitor (Siemens Sirecrust model 743G) and end-expired concentrations were maintained at 0.6–1.0%. Routine monitoring included ECG, pulse oximetry, capnography and non-invasive arterial

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pressure measurements (Datex Cardiocap, Datex Inc., Finland).

At the start of wound closure, patients received tramadol 3 mg kg^{-1} or morphine 0.2 mg kg^{-1} i.v. The drug was diluted to 5 ml by an anaesthetist who was not one of the observers. In order to compare the acute haemodynamic effects of i.v. administration of tramadol 3 mg kg^{-1} with morphine 0.2 mg kg^{-1}, measurements of arterial pressure and heart rate were documented before administering the drug and thereafter at 1, 5, 10 and 15 min after injection.

Also, at the start of wound closure, end-expired enflurane concentrations were decreased to 0.5% and ventilation minute volume reduced to allow end-tidal carbon dioxide partial pressure to increase to 5.5 kPa. Residual neuromuscular block was antagonized with glycopyrrolate 0.008 mg kg^{-1} and neostigmine 0.03 mg kg^{-1}. At the last skin-stitch, the anaesthetic gases were discontinued and a fresh gas flow of 6 litre min^{-1} was administered. The trachea was extubated on awakening while breathing spontaneously after which patients were transported to the recovery area where they were monitored for at least 90 min.

Time to commencement of spontaneous respiration, time to awakening as judged by the patient responding to the command "open your eyes", and time to orientation (as judged by being able to respond correctly to the question "When is your birthday") were recorded in the operating room.

In the recovery area, all patients received 35% oxygen by mask. Pain intensity was assessed by the patient and anaesthetist on arrival in the recovery room and every 15 min thereafter using a visual analogue scale (0=no pain, 10=worst possible pain). In addition, the presence of nausea and/or vomiting was recorded and the success of antiemetic therapy noted. The extent of respiratory depression was assessed by measurement of arterial blood-gas tensions on arrival in the recovery room and by measuring ventilatory frequency every 15 min. Arterial blood was obtained by radial artery puncture into a heparinzed syringe, and a Stat Profile Ultra apparatus (Nova Biomedicals, MA, USA) was used to measure blood-gas partial pressures. Recovery of psychomotor function was assessed in the recovery room using the p-deletion test at 15-min intervals. Patients who requested additional pain relief were given morphine 0.15 mg kg^{-1} i.m. Nausea was treated with metoclopramide 10 mg i.v. Data were recorded for 90 min in the recovery area or until patients received additional analgesia.

DATA ANALYSIS

A 5-min time difference for regaining consciousness between groups was regarded as clinically significant (SD 5 min). Assuming an alpha value of 0.05, a sample size of 17 was calculated to be required for a power of 0.8 for the *t* test. Each individual's p-deletion tests were standardized by comparing with preoperative values and calculating the "speed"[8] (i.e. speed=100×(No. of p's deleted)/(preoperative count)).

Statistical analysis was performed using a software package (Sigmastat for DOS version 5, Jandel Scientific Software, USA). Each patient's rate of recovery of cognitive function was assessed by determining the slope of the linear regression equation of p-deletion scores *vs* time. Inter-group comparisons were performed using unpaired two-tailed *t* tests. Pain scores were compared using the Mann–Whitney non-parametric test.

Results

Patient characteristics are presented in table 1. The two groups were comparable in age, weight, length and duration of anaesthesia. Tramadol 3 mg kg^{-1} or morphine 0.2 mg kg^{-1} administered during anaesthesia did not cause changes in arterial pressure or heart rate (table 2). In the operating room there were no differences in times to spontaneous respiration, awakening or orientation (table 3).

On arrival in the recovery room, blood-gas tensions, ventilatory frequency and pain scores were similar in the two groups (table 4). Ventilatory frequencies and pain scores remained similar in the two groups throughout the 90-min observation period (table 5). Six patients in the tramadol group and eight patients in the morphine group required supplementary analgesia at 59 (SD 19) min and 69 (24) min, respectively (ns between groups) (table 4). Four and two patients suffered nausea in the tramadol and morphine groups, respectively (Fisher's exact test, P=0.42).

The baseline p-deletion counts were similar in the two groups (table 6). No patient was able to perform p-deletion tests on arrival in the recovery room or 15 min thereafter. In both groups the number of capable

Table 1 Patient data (mean (SD or range)) in the two groups

Variable	Tramadol	Morphine	95% CI of difference	*t* test	
				t	*P*
Age (yr)	38.2 (8.0)	41.9 (10.9)	–2.5 to 9.8	1.21	0.23
Length (m)	1.56 (0 09)	1.59 (0.05)	–0.02 to 0.07	1.0	0.32
Mass (kg)	64.7 (14.5)	69.4 (18.8)	–61 to 15.4	0.88	0.39

Table 2 Mean arterial pressure (MAP) and heart rate (HR) changes after administration of tramadol or morphine during wound closure (mean (SD))

Time (min)	MAP (mm Hg)		HR (beat min^{-1})	
	Tramadol	Morphine	Tramadol	Morphine
0	93.1 (16.2)	91.6 (15.2)	76 (12)	75 (11)
1	90 6 (14)	89.2 (15.3)	71 (15)	77 (12)
5	90 3 (12.6)	87.6 (11.4)	73 (16)	78 (12)
10	98 (16.1)	95.3 (13.9)	81 (14)	81 (9)
15	92.5 (12.6)	99.2 (15 1)	75 (13)	81 (16)

Table 3 Operating room times (mean (SD) in the morphine and tramadol groups

Variable	Tramadol	Morphine	95% CI of difference	*t* test *t*	 *P*
Duration of anaesthesia (min)	102.8 (34.7)	96.9 (37.0)	–28.8 to 17.0	0.52	0.61
Time taken for wound closure (min)	10.6 (3.7)	12.7 (6.4)	–5.5 to 1.4	1.22	0.23
Time to spontaneous respiration (min)	3.2 (2.7)	4.1 (2.3)	–0.7 to 2.5	1.13	0.27
Time to awakening (min)	7.8 (4.0)	8.3 (3.7)	–2.0 to 3.0	0.41	0.68
Time to orientation (min)	17.9 (8.8)	18.9 (8.4)	–4.5 to 6.5	0.37	0.72

Table 4 Recovery room measurements (mean (SD) in the tramadol and morphine groups. Slope of recovery = slopes of the linear regression equations of p-deletion scores *vs* time

Variable	Tramadol	Morphine	95% CI of difference	*t* test *t*	 *P*
Pa_{O_2} (kPa)	16.0 (7.1)	16.3 (3.7)	–3.3 to 3.9	0.15	0.88
Pa_{CO_2} (kPa)	5.7 (0.7)	5.6 (0.6)	–0.4 to 0.4	0.1	0.92
Slope of recovery (No. min^{-1})	0.44 (0.2)	0.28 (0.2)	–0.31 to –0.01	2.18	0.036
Time to supplementary analgesia (min)	59.3 (19.3) (*n* = 6)	68.9 (24.2) (*n* = 8)	–11.6 to 30.8	0.95	0.35

Table 5 Postoperative ventilatory frequencies and pain scores (median (25–75th percentiles) [number of patients])

Variable	Time	Tramadol	Morphine	*P*
Ventilatory frequency (bpm)	Baseline	19 (17–22) [20]	19 (16–20) [20]	0.5
	15 min	20 (16–20) [20]	19 (16–20) [20]	0.71
	30 min	20 (16–20) [20]	18 (16–20) [20]	0.34
	45 min	20 (18–20) [20]	18 (17–20) [20]	0.14
	60 min	20 (18–20) [14]	18 (17–20) [16]	0.2
	75 min	18 (18–20) [15]	18 (16–20) [13]	0.23
	90 min	19 (17–20) [14]	18 (16–20) [12]	0.32
Pain score	15 min	5 (4.4–6.3) [5]	6 (5–8) [10]	> 0.1
	30 min	5 (3.5–6.8) [15]	6.5 (4–8) [18]	0.28
	45 min	6 (5–8) [18]	6 (4.0–7.5) [19]	0.63
	60 min	5.5 (4.5–7.5) [16]	5.5 (3.0–7.8) [14]	0.79
	90 min	5 (4.0–7.5) [15]	5 (4–7) [13]	0.77

patients increased with time and their scores improved. At 30 min after arrival, five patients in the tramadol group and four in the morphine group could do the tests and their performances were similar. At 45, 75 and 90 min, p-deletion counts and speed were greater in the tramadol group. The group mean of the slopes of the regression lines of each patient's p-deletion scores *vs* time was greater in the tramadol group. At 90 min, no patient was able to match their preoperative performance.

Discussion

Patients were deliberately anaesthetized lightly (0.5% enflurane in 60% nitrous oxide) until the last skin stitch was applied in order to determine if tramadol would accelerate recovery from anaesthesia. In a previous study[2] we administered tramadol 100 mg and 200 mg during light isoflurane–nitrous oxide anaesthesia and found that tramadol caused significant dose-dependent activation of the EEG for at least 20 min, evidenced by increased EEG frequencies and decreased amplitudes. These changes were small and the derived EEG variables did not approach values known to be associated with near awakening during anaesthesia. In view of these facts, we surmised that a greater dose may generate sufficient arousal to hasten recovery from anaesthesia and we administered up to twice the largest dose of our previous study. This did not lead to more rapid emergence from anaesthesia or to earlier orientation. Therefore, our present findings support our previous conclusion that tramadol does not cause clinically significant lightening of anaesthesia. The significance of our previous finding of EEG activation by tramadol[2] is difficult to interpret. It is a well known phenomenon, however that certain hypnotics (e.g. midazolam, thiopental, etomidate) exhibit a biphasic response, causing EEG activation in low doses (in spite of subjects being sedated or even asleep) before leading to EEG depression.[9–12]

Duration of wound closure was similar in both groups so that it is unlikely that it could have had significant influence on postoperative measurements of

Table 6 P-deletion scores obtained in the recovery area (mean (SD) [number of patients])

Variable	Time	Tramadol	Morphine	95% CI of difference	*t* test	
					t	*P*
P-deletion count	Pre-operative baseline	54 (14) [20]	51 (20) [20]	−15 to 7	0.7	0.49
	30 min	9 (8) [5]	2 (1) [4]	−17 to 3	1.6	0.15
	45 min	23 (20) [9]	5 (4) [9]	−32 to −3	2.6	0.02
	60 min	21 (20) [12]	8 (7) [12]	−25 to 0	2.0	0.53
	75 min	29 (23) [12]	11 (12) [15]	−23 to −1	2.2	0.04
	90 min	32 (20) [12]	17 (12) [14]	−28 to −2	2.3	0.029
Speed (%)	30 min	15 (14) [5]	5 (3) [4]	−27 to 8	1.34	0.22
	45 min	37 (32) [9]	10 (5) [9]	−50 to 4	2.5	0.22
	60 min	38 (32) [12]	18 (16) [12]	−41 to 2	1.9	0.068
	75 min	42 (27) [12]	23 (21) [15]	−38 to 0	2.1	0.048
	90 min	53 (30) [12]	32 (18) [14]	−40 to −1	2.2	0.042

recovery. Furthermore, administration of nitrous oxide and enflurane was continued up until the time of the last stitch in order to standardize the timing of the recovery process, thereby eliminating the influence of variation in the duration of wound closure. Tramadol or morphine was administered at the beginning of closure of the peritoneum, at which time end-expired enflurane concentrations were targeted at 0.5%. This was done for two reasons: first, as both morphine and tramadol are reputed to be somewhat slow-acting, we reasoned that at the end of wound closure, the drugs would be exerting maximum effects. Second, we normalized the recovery process by ensuring that the partial pressures of the anaesthetic gases were the same in all patients at the start of drug excretion.

Additional evidence to support the conclusion that tramadol does not antagonize the hypnotic effects of anaesthetic gases is provided by the finding that for the first 15 min after arrival in the recovery room, all patients in both groups were unable to perform p-deletion tests. At 30 min only approximately 50% of patients in both groups were sufficiently alert to accomplish p-deletions. It is likely that during this early recovery phase, patients were encountering residual effects of enflurane and we suggest that if tramadol opposed the effects of the anaesthetic, the tramadol group would have performed better.

After 45 min in the recovery room, all patients in the tramadol and morphine groups were able to perform the p-deletion tests. From this time onwards, the tramadol patients had more rapid recovery of psychomotor function as evidenced by the greater slopes of their regression lines of p-deletions *vs* time and by their greater p-deletion counts and speed. This tendency towards more rapid recovery of psychomotor function is in agreement with the study of Vickers and colleagues[13] who compared tramadol with morphine for postoperative pain after abdominal surgery and found that there was a tendency to better recovery in those patients who received tramadol. This should not be interpreted as an indication that tramadol caused increased alertness, but rather that it caused less sedation than morphine.

Tramadol is reputed to cause less respiratory depression than morphine.[3] However, in our study, times to commencement of breathing in the operating room, blood-gas partial pressures on arrival in the recovery room and breathing rates were similar. Therefore, it appears that the two agents did not exert different effects on respiration after operation. This may perhaps be a result of the continuing depressant effects of enflurane masking any differences that may have existed in the the immediate postoperative period. It is possible that more sensitive tests of the respiratory centre (e.g. carbon dioxide dose–response curves) would have detected a minor difference, however, the difference is not likely to have been clinically relevant. Pulse oximetry was not used as a measure of respiratory depression because all patients were breathing high oxygen concentrations and would have most likely remained well oxygenated in spite of moderate hypoventilation.

Our tramadol dose of 3 mg kg^{-1} was higher than previously recommended doses for pain relief after abdominal surgery. There is considerable variation in the doses that have been found to be effective in previous studies. Houmes and colleagues[3] administered a maximum of 150 mg in three divided doses over 6 h and found this to be insufficient for patients experiencing severe pain. Vickers and colleagues[13] administered greater doses; an initial dose of 100 mg followed by a flexible dosing regimen, providing up to 100–250 mg in the first 90 min and 650 mg during the first 24 h. The initial bolus provided sufficient pain relief in only 12.5% of patients and the overall responder rate was only 72.6%. During the first 1.5 h, patients required 188.2 mg. The authors concluded that adequate dosing in the early postoperative phase is important and that relief of pain after abdominal surgery is indistinguishable from that of morphine if given in appropriate i.v. doses. Therefore, we suggest that the greater tramadol dose (3 mg kg^{-1}) that we used is more suitable for treatment of postoperative pain, causing minimal side effects.

Tramadol, a weak mu-agonist, has not been shown to potentiate the effects of anaesthetics and therefore it is generally not recommended as an adjunct to anaesthetic agents during surgery. It is our practice, however, to administer analgesics during the final stages of a surgical procedure to ensure that patients have basic pain relief during the immediate postoperative phase. Used in this way at a dose of 3 mg kg^{-1}, our study indicated that tramadol was as effective as morphine for controlling pain in the immediate postoperative period, without any increase in the incidence of nausea and vomiting or cardiovascular changes. Furthermore, there was a more rapid rate of recovery of psychomotor function probably caused by the lack of significant sedating effects. We suggest therefore that tramadol has a useful role in anaesthetic practice, particularly for day-surgery where rapid return to normal activities is desired.

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References

1. Lehmann KA, Horrichs G, Hoeckle W. Zur Bedeutung von Tramadol als intraoperativem Analgetikum Eine randomisierte Doppelblindstudie im Vergleich zu Placebo [The significance of tramadol as an intraoperative analgesic. A randomized double-blind study in comparison with placebo.] *Anaesthesist* 1985; 34: 11–19.
2. Coetzee JF, Maritz JS, du Toit C. Effect of tramadol on depth of anaesthesia. *British Journal of Anaesthesia* 1996, 76: 415–418.
3. Houmes RJ, Voets MA, Verkaaik A, Erdmann W, Lachmann B Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. *Anesthesia and Analgesia* 1992; 74: 510–514
4. Lee CR, McTavish D, Sorkin EM. Tramadol A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs* 1993, 46: 313–340.
5. Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. *Anaesthesia* 1992; 47: 291–296.
6. Striebel HW, Hackenberger J. Comparison of tramadol/metamizole infusion versus combined tramadol infusion and ibuprofen suppositories for postoperative pain management after hysterectomy. *Anaesthesist* 1992; 41: 354–360.
7. Dixon RA, Thornton JA. Tests of recovery from anaesthesia and sedation: intravenous diazepam in dentistry. *British Journal of Anaesthesia* 1973, 45: 207–215.
8. Cashman JN, Power SJ. An evaluation of tests of psychomotor function in assessing recovery following a brief anaesthetic. *Acta Anaesthesiologica Scandinavica* 1989, 33: 693–697.
9. Brown CR, Sarnquist FH, Canup CA, Pedley TA. Clinical, electroencephalographic, and pharmacokinetic studies of a water-soluble benzodiazepine, midazolam maleate. *Anesthesiology* 1979; 50: 467–470
10. Veselis RA, Reinsel R, Alagesan R, Heino R, Bedford RF. The EEG as a monitor of midazolam amnesia: changes in power and topography as a function of amnesic state. *Anesthesiology* 1991; 74: 866–874.
11. Buhrer M, Maitre PO, Hung OR, Ebling WF, Shafer SL, Stanski DR. Thiopental pharmacodynamics I. Defining the pseudo-steady-state serum concentration–EEG effect relationship. *Anesthesiology* 1992; 77: 226–236.
12 Ghoneim MM, Yamada T. Etomidate: a clinical and electroencephalographic comparison with thiopental *Anesthesia and Analgesia* 1977; 56: 479
13. Vickers MD, Paravicini D Comparison of tramadol with morphine for post-operative pain following abdominal surgery *European Journal of Anaesthesiology* 1995; 12: 265–271

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Comparison of the analgesic potency of xenon and nitrous oxide in humans evaluated by experimental pain

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Summary

We have compared the analgesic potency of MAC-equivalent concentrations of xenon (10, 20, 30 and 40%) and nitrous oxide (15, 30, 45 and 60%) in humans using a multimodal experimental pain testing and assessment technique. We tested 12 healthy volunteers in a randomized, single-blind, crossover study. The following experimental pain tests were used: nociceptive reflex to repeated stimuli; pain tolerance to maximal effort tourniquet ischaemia; electrical stimulation; mechanical pressure; and cold. Reaction time was also measured. Xenon and nitrous oxide produced analgesia to ischaemic, electrical and mechanical stimulation, but not to cold pain. There was no difference in MAC-equivalent concentrations of xenon and nitrous oxide. Both increased reaction time in a similar manner. Xenon and nitrous oxide evoked nausea and vomiting in a large number of volunteers. (*Br. J. Anaesth.* 1998; **81**: 742–747).

Keywords: anaesthetics gases, nitrous oxide; anaesthetics gases, xenon; pain, experimental

The anaesthetic properties of xenon in humans were first reported by Cullen and Gross in 1951.[1] Xenon possibly has a future as an anaesthetic, replacing nitrous oxide.[2] In contrast with nitrous oxide, xenon is non-toxic and probably metabolically inert. Nitrous oxide can be a health hazard after prolonged exposure to low concentrations.[3–5] Nitrous oxide is teratogenic in rats, whereas xenon is not.[6] Also, xenon is harmless to the ozone layer and probably more potent than nitrous oxide.[7 8] The main limiting factor for the widespread use of xenon has been its very high cost. However, costs can be reduced using anaesthetic machines with recycling systems for xenon.

A recent study[9] showed no statistically significant difference in the analgesic effects of 0.3 MAC of xenon (21%) and nitrous oxide (30%).[10 11] However, only a small number of volunteers were studied (n=6) and only pain thresholds to heat stimulations were measured. Utsumi and colleagues[12] found that 70% xenon and 70% nitrous oxide suppressed spinal cord dorsal horn neurones to a similar degree, with no significant difference between the two agents.

The importance of using a multimodal testing and assessment technique can be demonstrated by the following example. Propofol in subanaesthetic concentrations increases the threshold of the nociceptive reflex to single stimulations.[13] If we compare this result with earlier studies with different analgesic drugs using the same stimulation methodology,[14–20] we could conclude that propofol has an analgesic effect. But propofol does not affect the threshold of the nociceptive reflex to repeated stimulations,[13] which would indicate that propofol, after repeated stimulations, does not have an analgesic effect. However, propofol reduces pain tolerance to mechanical pressure, indicating a hyperalgesic effect on mechanical pressure.[13]

The aim of our study was to use a multimodal experimental pain testing and assessment technique to compare the analgesic potency of xenon and nitrous oxide in humans.

Subjects and methods

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Bern, and written informed consent according to the Helsinki Declaration was obtained. We studied 12 healthy volunteers (median age 24.0 (range 22–30 yr)), who were not receiving any medications, had no allergies or previous adverse reactions to anaesthesia in a randomized, single-blind, crossover study. Female volunteers were excluded if they were pregnant. They were investigated on two different days with at least a 48-h interval. Because of logistical reasons (separate anaesthetic machines and gas analysers for xenon and nitrous oxide), volunteers could not be blinded to the person carrying out the tests, but were blinded to the gas used.

To minimize the risk of acid aspiration, volunteers were tested after a fasting period of at least 6 h, and before testing they received ranitidine 150 mg dissolved in water. During testing, volunteers rested comfortably in the supine position. An i.v. infusion of saline was started and haemoglobin oxygen saturation by pulse oximetry, ECG and non-invasive arterial pressure were monitored continuously during the experiment. Subanaesthetic gas concentrations were delivered via a face mask fastened with conventional

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rubber straps. Inspiratory and expiratory gases were sampled close to the nostrils via a plastic tube fitted through a hole drilled in the mask. Inspired and end-tidal nitrous oxide, oxygen and carbon dioxide concentrations were analysed using a Capnomac Ultima (Datex, Helsinki, Finland) and stored on a personal computer. Inspired xenon was analysed using a mass spectrometer (Xenotec 2000, Leybold, Köln, Germany). The gas monitors were calibrated before each investigation. The following experimental tests were applied in the order listed below.

NOCICEPTIVE REFLEX TO REPEATED STIMULI

The sural nerve was stimulated behind the right lateral malleolus via surface electrodes filled with electrode gel (inter-electrode distance approximately 3 cm). A 25-ms stimulus (in reality a train-of-five 1-ms square wave impulses, which is perceived as a single stimulus) was repeated five times with a frequency of 2 Hz.[21] Electromyographic (EMG) reflex responses were recorded with surface electrodes placed over the middle of the biceps femoris and rectus femoris. Current intensity was increased from 1–2 mA in steps of 1–2 mA until summation in the reflex response was observed. Summation was defined as an increase in amplitude of the fourth and/or fifth reflexes of at least 50% compared with the first and/or second reflexes.[20 22 23] The summation threshold was defined as the minimal current intensity that could repeatedly elicit a summation response in the EMG.

ISCHAEMIC PAIN TOLERANCE

Pain tolerance to maximal effort tourniquet ischaemia was used.[24] An arterial pressure cuff was placed on the right arm. The volunteer exercised at maximal effort with a calibrated handgrip trainer at a strength of 25 pounds for 2 min. The cuff was then immediately inflated and the pressure kept constant at 250 mm Hg for a maximum of 2 min. If pain was considered intolerable before 2 min had elapsed, the volunteer could verbally indicate this. The elapsed time was noted, and the cuff was deflated. Perceived pain intensity was rated continuously using an electronic visual analogue scale (VAS) and recorded on a personal computer. Duration of ischaemia, peak pain and area under the pain intensity–time curve were determined. If the cuff was deflated before the end of 2 min, pain intensity was considered to be maximal until the end of the period (for calculation of area under the curve).

ELECTRICAL PAIN TOLERANCE

A 1-mm diameter intracutaneous electrode[25] was applied to the second toe of the left foot. Intracutaneous placement was accepted if the sensory threshold was less than 0.5 mA. Electrical pain tolerance thresholds were determined with a 25-Hz train of 0.5-ms constant-current square wave pulses of increasing intensity (0.01 mA per stimulation, maximum intensity 10 mA) delivered from a computer-controlled stimulator (University of Aalborg, Denmark). The volunteer was instructed to press a button when the pain became intolerable. The current intensity at this point was recorded and defined as the electrical pain tolerance threshold. Four stimulations were given (inter-stimulus interval 10–20 s) and the average of the last three determinations was calculated.

PRESSURE PAIN TOLERANCE

Pressure pain tolerance thresholds were determined on the centre of the pulp of the second and third finger of the left hand with an electronic pressure algometer (Somedic AB, Stockholm, Sweden).[20 22 26–29] A probe with a surface area of 0.28 cm^2 was used, and the pressure increase was set to 30 $kPa\ s^{-1}$. Pain tolerance was defined as the point when the volunteer did not want the pressure to be increased further. For determination of the threshold, the mean of two consecutive measurements was used.

COLD PAIN TOLERANCE

A 2-min ice water test was used.[20 22 30 31] Before immersion, the skin temperature on the thenar of the left hand was measured and if it was less than 30.0 °C, the hand was warmed until skin temperature was more than 30.0 °C. The left hand was then immersed in ice saturated water (1.5±1.0 °C) which was stirred continuously during immersion. If pain was considered intolerable before 2 min had elapsed, the volunteer could withdraw the hand, and the elapsed time was noted. Perceived pain intensity was rated continuously with an electronic visual analogue scale (VAS) and recorded on a personal computer. Duration of immersion, peak pain and area under the pain intensity–time curve were determined. If the hand was withdrawn before the end of 2 min, pain intensity was considered to be maximal until the end of the 2-min period (for calculation of area under the curve).

REACTION TIME

A 1000-Hz tone was delivered from a computer with randomized intervals of 3–8 s, and a timer started simultaneously. The volunteer was told to press a button as fast as possible after each tone. Reaction time was defined as the time from the tone until the volunteer pressed the button. The mean of five consecutive measurements was used.

The pain tests were explained to the volunteer and a trial testing of all techniques was performed in order to familiarize the volunteer with the procedure. The mask was then fitted until the volunteer felt comfortable, and there were no leaks. Thereafter the volunteer breathed oxygen for a minimum of 5 min via a semi-closed breathing system (Cicero EM Xenon, Dräger, Lübeck, Germany).

PROCEDURE

A baseline test series of the above tests was performed. Thereafter, according to the randomization, xenon or nitrous oxide in MAC-equivalent concentrations[10 11] was introduced slowly into the breathing system (fresh gas flow 3 litre min^{-1}) and adjusted to the first concentration. For xenon, volunteers received 10, 20, 30 and 40% (inspired), and for nitrous oxide 15, 30, 45 and 60% (end-tidal). We had planned to randomize whether the gases should be given in an ascending or descending order, but one of the authors in a pilot study vomited within 5 min after receiving 50% nitrous oxide, and the first volunteer given nitrous oxide in a descending series also vomited after receiving 60% which prevented completion of the experiment. Thereafter, all gas concentrations were given in ascending order.

Testing was started after a 10-min equilibration period at constant inspired (xenon) or end-tidal (nitrous oxide) concentrations. After testing had been performed at all four concentrations, the gas was discontinued. A final post-gas test series was performed after the volunteer had breathed oxygen via the mask for 30 min. At the two lowest concentrations of xenon and nitrous oxide and at the post-gas test series, all experimental tests were performed (duration of test series 15–18 min). At the two highest concentrations of xenon and nitrous oxide, ischaemic pain and cold pain tolerance were not determined, as these require a higher degree of co-operation than pressing a button when the pain becomes intolerable (duration of test series 5–8 min). The inspired to end-tidal nitrous oxide concentration difference during the last 5 min of each equilibration period was later calculated from the stored data.

Statistical analysis was performed independently for each pain test. The numerical values for each measurement were transformed to percentage of baseline measurements. To determine if there was a statistically significant trend over concentrations, the Page test for ordered alternatives was used for each pain test and gas. For each pain test, the assumed equi-effective concentrations of xenon and nitrous oxide were compared using the Wilcoxon signed ranks matched pairs test. The Wilcoxon test was also used to test for an effect of time on each pain test by comparing baseline with post-gas measurements for each gas. $P<0.05$ was considered significant.

Results

For the two lowest concentrations of xenon (10 and 20%) and nitrous oxide (15 and 30%), testing was performed in 11 of the 12 volunteers. One volunteer developed myoclonia-like side effects after administration of 20% xenon, and further administration of xenon was stopped. Because of nausea and vomiting, testing was only possible in a few volunteers at 45% xenon and 60% nitrous oxide, and therefore statistical analysis could not be performed at the highest concentration. For the nociceptive reflex to repeated stimulations, statistical analysis was performed at the three remaining concentrations; for all other tests, analysis was performed at the two lowest gas concentrations. Figure 1 summarizes the results for 20% xenon and 30% nitrous oxide.

The nociceptive reflex to repeated stimuli was tested in eight volunteers at three concentrations of xenon (10, 20, 30%) and three concentrations of nitrous oxide (15, 30, 45%) (table 1). There was a significant trend for an increase in the threshold to nociceptive reflex to repeated stimulations for increasing concentrations of both xenon ($P<0.001$) and nitrous oxide ($P<0.001$). There was no significant difference between MAC-equivalent concentrations of xenon and nitrous oxide.

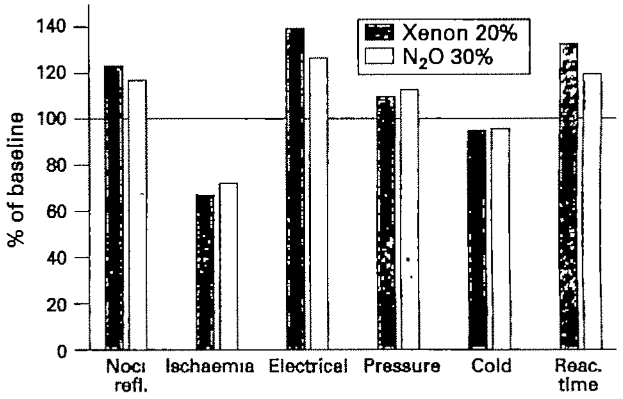

Figure 1 Effects of 20% xenon and 30% nitrous oxide (N_2O) on the nociceptive reflex (Noci. refl.), ischaemic pain tolerance (area under the pain intensity–time curve), electrical pain, pressure pain tolerance, cold pain tolerance (area under the pain intensity–time curve) and reaction time. Results are expressed as percentage of baseline values.

For increasing concentrations of both xenon and nitrous oxide, there was a significant trend in (table 2): (1) reduction in the area under the pain intensity–time curve for ischaemia (xenon $P<0.001$, nitrous oxide $P<0.001$) but not for cold; (2) reduction of the maximal or peak pain intensity for ischaemia (xenon $P<0.05$, nitrous oxide $P<0.01$) but not for cold; (3) increase in duration of cold (xenon $P<0.05$, nitrous oxide $P<0.01$) but not ischaemic pain; (4) increase in electrical (xenon $P<0.001$, nitrous oxide $P<0.01$) and mechanical pressure (xenon $P<0.01$, nitrous oxide $P<0.001$) pain tolerance; and (5) increase in reaction time (xenon $P<0.001$, nitrous oxide $P<0.001$).

There was a significant difference between the reduction in the area under the ischaemic pain intensity–time curve for 10% xenon and 15% nitrous oxide ($P<0.05$) and in the difference between the increase in electrical pain tolerance for 10% xenon and 15% nitrous oxide ($P<0.05$), and for 20% xenon and 30% nitrous oxide ($P<0.02$).

Except for sensory threshold ($P<0.05$) and pain tolerance ($P<0.05$) to electrical stimulation, and duration of immersion in iced water for nitrous oxide ($P<0.02$), there was no effect of time (post-gas values were not significantly different from baseline) on the pain tests (table 3).

The inspired to end-tidal nitrous oxide concentration difference during the last 5 min of each equilibration period was not more than 1%.

Of the 11 volunteers tested with both xenon and nitrous oxide, nine experienced nausea at 30% xenon and seven at 45% nitrous oxide. Vomiting occurred in six volunteers after 30% xenon and in six after 45% nitrous oxide.

Discussion

Our study showed that xenon and nitrous oxide attenuated pain induced with different modalities in a similar manner, indicating that they have similar analgesic profiles. The analgesic potency of xenon was approximately 1.5 times higher than that of nitrous oxide. Both xenon and nitrous oxide evoked nausea and vomiting in a large number of volunteers.

The MAC values of xenon and nitrous oxide have

Table 1 Numerical results for the nociceptive reflex to repeated stimulations. All values are median (25–75 percentiles), and are expressed as percentage of baseline values (baseline = 100%). There was a significant trend for increasing concentrations of both xenon and nitrous oxide

Xenon		Nitrous oxide	
Concentration	% of baseline	Concentration	% of baseline
10%	114.3 (100.0–120.0)	15%	100.0 (100.0–121.7)
20%	122.5 (100.0–130.8)	30%	116.7 (102.5–126.4)
30%	150.0 (100.0–164.2)	45%	140 0 (115.7–152 9)

Table 2 Numerical results for the experimental pain tests and reaction time. All values are median (25–75 percentiles), and are expressed as percentage of baseline values (baseline = 100%). *$P<0.05$ for a significant trend for increasing concentrations of both anaesthetics

	Xenon		Nitrous oxide	
Test	10%	20%	15%	30%
Ischaemic pain tolerance–peak pain *	93.3 (52.9–100.0)	93.4 (50.0–100.0)	100.0 (77.6–100.0)	79.8 (36.9–97.4)
Ischaemic pain tolerance–AUC *	72.5 (42.4–94.8)	67.1 (55.7–73.7)	94.7 (82.1–98.8)	71.9 (30.9–87.4)
Electrical–pain tolerance *	130.6 (111.0–146.5)	138.7 (122.5–219.0)	112.6 (102.1–117.20)	126.2 (112.1–171.9)
Mechanical pressure–pain tolerance *	106.8 (105.6–111.7)	109.7 (103.1–122.1)	105.4 (101.1–109.4)	112.4 (106.1–116.4)
Cold pain tolerance–duration of immersion *	112.5 (103.0–126.5)	119.6 (100.0–148.5)	106.6 (100.0–112.5)	121.0 (100.0–158.5)
Cold pain tolerance–peak pain	100.0 (100.0–100.0)	100.0 (94.7–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)
Cold pain tolerance–AUC	98.6 (91.2–101.6)	94.8 (84.3–98 6)	99.5 (98.0–103.9)	95.7 (93 9–97 6)
Reaction time *	106.3 (87.4–131.3)	132.5 (123.2–143.8)	100.0 (92.4–116.7)	119.8 (109.5–178 2)

Table 3 Effect of time on the pain test was assessed by comparing post-gas values with baseline. All values are median (25–75 percentiles), and are expressed as percentage of baseline values (baseline = 100%). *$P< 0.05$

Test	Xenon	Nitrous oxide
Temporal summation	100.0 (100.0–125.0)	113.9 (100 0–120.0)
Ischaemic pain tolerance–duration	100.0 (100.0–100.0)	100.0 (100.0–111.9)
Ischaemic pain tolerance–peak pain	100.0 (90.8–100.0)	100.0 (76.6–100.0)
Ischaemic pain tolerance–AUC	96.4 (90.1–102.4)	95.5 (82.6–104.1)
Electrical–pain tolerance	112.5 (86.1–126.4)	111.1 (100.0–138.6) *
Electrical–pain sensory threshold	133.3 (100.0–150.0)	133 3 (100.0–162.5) *
Mechanical pressure–pain tolerance	99.3 (86.7–105.9)	97.9 (92.5–102 9)
Cold pain tolerance–duration of immersion	81.8 (76.3–100.0)	91.9 (75.4–100.0) *
Cold pain tolerance–peak pain	100.0 (100.0–100.0)	100.0 (100.0–102.8)
Cold pain tolerance–AUC	104.4 (102.1–110.4)	103.2 (99.4–108.7)
Reaction time	100.0 (100.0–125.0)	113.9 (100.0–120.0)

been reported to be 70%[10] and 105%,[11] respectively. Xenon is therefore 1.5 times more effective in depressing gross purposeful movement to skin incision than nitrous oxide. In our study, 1.5 times greater concentrations of nitrous oxide were compared with xenon. In no test was nitrous oxide more effective than xenon, but xenon increased pain tolerance to electrical stimulation significantly more than MAC-equivalent doses of nitrous oxide. The significant difference between 10% xenon and 15% nitrous oxide for area under the pain intensity–time curve for ischaemic pain, and the slight decrease in duration of immersion in iced water at the post-gas measurement for nitrous oxide could be a result of chance, as the probability of a type I error increases with increasing number of comparisons between concentrations. The small but significant increase in electrical pain tolerance at the post-gas measurement was probably a result of a simultaneous increase in the sensory threshold. Cullen and Gross,[1] using heat pain thresholds, found a 15% increase in pain thresholds with both gases (50% xenon and 50% nitrous oxide). Yagi and colleagues[9] found no statistically significant difference in the analgesic effects of 0.3 MAC of xenon (21%) and nitrous oxide (30%). However, only a small number of volunteers were studied ($n=6$), and only pain thresholds to heat stimulation were measured. In their study, 21% xenon increased the response time four times more than 30% nitrous oxide, indicating that the sedative–hypnotic potency of xenon is more than 1.5 times that of nitrous oxide. Our study supports this assumption, as we also found that 20% xenon increased reaction time (similar to the response time of Yagi and co-workers) more than 30% nitrous oxide. Utsumi and colleagues[12] found that 70% xenon and 70% nitrous oxide suppressed spinal cord dorsal horn neurones to a similar degree, indicating no statistically significant difference in the direct spinal effects of xenon and nitrous oxide.

For equilibration of nitrous oxide, end-tidal concentrations were used as these can be measured easily with conventional anaesthetic gas analysers. Xenon cannot be measured with conventional anaesthetic gas analysers. In our study, a mass spectrometer was used. As this was not prepared for breath-to-breath end-tidal measurements, we could only measure inspired concentrations of xenon. However, the blood–gas solubility of xenon is 0.14 compared with 0.47 for nitrous oxide. Therefore, because of the fast kinetics of xenon and a fresh gas flow of 3 litre min^{-1}, a 10-min equilibration period should ensure an end-tidal xenon concentration close to fresh gas concentrations. For nitrous oxide, the inspired to end-tidal concentration difference during the last 5 min of each equilibration period was not more than 1%. The actual xenon concentrations might have been slightly lower than intended. This would further support the assumption that the analgesic potency of xenon is higher than 1.5 times that of nitrous oxide.

The high incidence of nausea and vomiting in our study with both xenon and nitrous oxide was surprising. After the first cases of nausea and vomiting, we learnt to recognize impending nausea and vomiting, and discontinued administration before nausea progressed to vomiting. The real incidence of vomiting could therefore be higher. Lorenz and colleagues[32] found no nausea with 33% xenon or Sclabassi and colleagues[33] with 25, 30 and 35% xenon. However, administration time was short in both studies. Several studies using up to 10 min administration of up to 50% nitrous oxide reported no nausea and vomiting.[34–36] Rupreht and colleagues[37] found a high incidence of nausea (six of eight volunteers) and vomiting (number not reported) in volunteers breathing 60–80% nitrous oxide for at least 45 min. In our volunteers, nausea quickly vanished after discontinuation of nitrous oxide or xenon. Nitrous oxide has been considered to contribute to postoperative nausea and vomiting,[38–42] as have inhalation anaesthetics and opioids.[38 39] Xenon would presumably also contribute to postoperative nausea and vomiting, but this has not been studied in depth. Xenon is a more potent analgesic than nitrous oxide and therefore the peroperative need for opioids is reduced.[7] Xenon might be a sufficiently potent hypnotic to allow omission of further inhalation agents. Therefore, the postoperative incidence of nausea and vomiting with xenon might be less than that with nitrous oxide.

Considering the beneficial effects of xenon on haemodynamic reactions[7 43 44] and catecholamine release,[7 44] and that the analgesic and probably the sedative–hypnotic potencies of xenon are at least 1.5 times higher than those of nitrous oxide, we believe that further investigations on xenon as an anaesthetic are warranted.

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References

1. Cullen SC, Gross EG. The anesthetic properties of xenon in animals and human beings, with additional observations on krypton. *Science* 1951; **113**: 580–582.
2. Lachmann B, Armbruster S, Schairer W, Landstra M, Trouwborst A, van Daal GJ, Kusuma A, Erdmann W. Safety and efficacy of xenon in routine use as an inhalational anaesthetic. *Lancet* 1990; **335**: 1413–1415.
3. Spence AA. Environmental pollution by inhalational anaesthetics. *British Journal of Anaesthesia* 1987; **59**: 96–103.
4. Dyck PJ, Grina LA, Lambert EH, Calder CS, Oviatt K, Rehder K, Lund BA, Skau KA. Nitrous oxide neurotoxicity studies in man and rat. *Anesthesiology* 1980; **53**: 205–209.
5. Cohen EN, Bellville JW, Brown BW. Anesthesia, pregnancy, and miscarriage: a study of operating room nurses and anesthetists. *Anesthesiology* 1971; **35**: 343–347.
6. Lane GA, Nahrwold ML, Tait AR, Taylor-Busch M, Cohen PJ, Beaudoin AR. Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. *Science* 1980; **210**: 899–901.
7. Boomsma F, Rupreht J, Man in 't Veld AJ, de Jong FH, Dzoljic M, Lachmann B. Haemodynamic and neurohumoral effects of xenon anaesthesia. A comparison with nitrous oxide. *Anaesthesia* 1990; **45**: 273–278.
8. Eger EI, Brandstater B, Saidman LJ, Regan MJ, Severinghaus JW, Munson ES. Equipotent alveolar concentrations of methoxyflurane, halothane, diethyl ether, fluroxene, cyclopropane, xenon and nitrous oxide in the dog. *Anesthesiology* 1965; **26**: 771–777.
9. Yagi M, Mashimo T, Kawaguchi T, Yoshiya I. Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide. *British Journal of Anaesthesia* 1995; **74**: 670–673.
10. Cullen SC, Eger EI, Cullen BF, Gregory P. Observations on the anesthetic effect of the combination of xenon and halothane. *Anesthesiology* 1969; **31**: 305–309.
11. Hornbein TF, Eger EI, Winter PM, Wetstone D, Smith KH. The minimum alveolar concentration of nitrous oxide in man. *Anesthesia and Analgesia* 1982; **61**: 553–556.
12. Utsumi J, Adachi T, Miyazaki Y, Kurata J, Shibata M, Murakawa M, Arai T, Mori K. The effect of xenon on spinal dorsal horn neurones: A comparison with nitrous oxide. *Anesthesia and Analgesia* 1997; **84**: 1372–1376.
13. Petersen-Felix S, Arendt-Nielsen L, Bak P, Fischer M, Zbinden AM. Psychophysical and electrophysiological responses to experimental pain may be influenced by sedation: comparison of the effects of a hypnotic (propofol) and an analgesic (alfentanil). *British Journal of Anaesthesia* 1996; **77**: 165–171
14. Willer JC. Comparative study of percived pain and nociceptive flexion reflex in man. *Pain* 1977; **3**: 69–80.
15. Chan CWY, Dallaire M. Subjective pain sensation is linearly correlated with the flexion reflex in man. *Brain Research* 1989; **479**: 145–150.
16. Willer JC. Studies on pain. Effects of morphine on a spinal nociceptive flexion reflex and related pain sensation in man. *Brain Research* 1985; **331**: 105–114.
17. Willer JC, Bergeret S, Gaudy JH. Epidural morphine strongly depresses nociceptive flexion reflexes in patients with postoperative pain. *Anesthesiology* 1985; **63**: 675–680.
18. Willer JC, Bathien N. Pharmacological modulations on the nociceptive flexion reflex in man. *Pain* 1977; **3**: 111–119
19. Willer JC, De Broucker T, Bussel B, Roby-Brami A, Harrewyn JM. Central analgesic effect of ketoprofen in humans: electrophysiological evidence for a supraspinal mechanism in a double-blind cross-over study. *Pain* 1989; **38**: 1–7.
20. Petersen-Felix S, Arendt-Nielsen L, Bak P, Bjerring P, Breivik H, Svensson P, Zbinden AM. Ondansetron does not inhibit the analgesic effect of alfentanil. *British Journal of Anaesthesia* 1994; **73**: 326–330.
21. Arendt-Nielsen L, Brennum J, Sindrup S, Bak P. Electrophysiological and psychophysical quantification of central temporal summation of the human nociceptive system. *European Journal of Applied Physiology* 1994; **68**: 266–273.
22. Petersen-Felix S, Bak P, Arendt-Nielsen L, Fischer M, Bjerring P, Roth D, Zbinden AM. Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by experimentally induced pain. *British Journal of Anaesthesia* 1995; **75**: 55–60.
23. Arendt-Nielsen L, Nielsen J, Petersen-Felix S, Schnider TW, Zbinden AM. Effect of racemic mixture and the (S+)-isomer of ketamine on temporal and spatial summation of pain. *British Journal of Anaesthesia* 1996; **77**: 625–631.
24. Maurset A, Skoglund LA, Hustveit O, Klepstad P, Iye I. A new version of the ischemic tourniquet pain test. *Methods and Findings in Experimental and Clinical Pharmacology* 1991; **13**: 643–647.
25. Bromm B, Meier W. The intracutaneous stimulus: a new pain model for algesimetric studies. *Methods and Findings in Experimental and Clinical Pharmacology* 1984; **6**: 405–410.
26. Brennum B, Kjeldsen M, Jensen K, Jensen TS. Measurement of human pressure-pain thresholds on fingers and toes. *Pain* 1989; **38**: 211–217.
27. Dahl JB, Rosenberg J, Molke Jensen F, Kehlet H. Pressure pain thresholds in volunteers and herniorrhaphy patients. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 673–676.

28. Brennum J, Arendt-Nielsen L, Secher NH, Jensen TS, Bjerring P Quantitative sensory examination in human epidural anaesthesia and analgesia: effects of lidocaine. *Pain* 1992; **51**: 27–34.
29. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesthesia and Analgesia* 1995; **81**: 63–68.
30. Sindrup SH, Poulsen L, Brøsen K, Arendt-Nielsen L, Gram LF. Are poor metabolisers of sparteine/debrisoquine less pain tolerant than extensive metabolisers? *Pain* 1993; **53**: 335–349.
31. Jones SF, McQuay HJ, Moore RA, Hand CW. Morphine and ibuprofen compared using the cold pressor test. *Pain* 1988; **34**: 117–122.
32. Lorenz M, Holl K, Nemati N, Haubitz B, Gaab MR, Dietz H. Effects of 33% stable xenon/O_2 mixture on somatosensory evoked potentials. *Neurological Research* 1991; **13**: 133–135.
33. Sclabassi RJ, Lofink RM, Guthkelch AN, Gur D, Yonas H. Effect of low concentration stable xenon on the EEG power spectrum. *Electroencephalography and Clinical Neurophysiology* 1987; **67**: 340–347.
34. Whitwam JG, Morgan M, Hall GM, Petrie A. Pain during continuous nitrous oxide administration. *British Journal of Anaesthesia* 1976; **48**: 425–429.
35. James MFM, Manson EDM, Dennett JE. Nitrous oxide analgesia and altitude. *Anaesthesia* 1982; **37**: 285–288.
36. Dworkin SF, Chen ACN, Schubert MM, Clark DW. Cognitive modification of pain: information in combination with N_2O. *Pain* 1984; **19**: 339–351.
37. Rupreht J, Dworacek B, Bonke B, Dzoljic MR, van Eijndhoven JHM, de Vlieger M. Tolerance to nitrous oxide in volunteers. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 635–638.
38. Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment, and prevention. *Anesthesiology* 1992; **77**: 162–184.
39. Kenny GNC. Risk factors for postoperative nausea and vomiting. *Anaesthesia* 1994; **49** (Suppl.): 6–10.
40. Tramèr M, Moore A, McQuay H. Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials *British Journal of Anaesthesia* 1996; **76**: 186–193.
41. Tramèr M, Moore A, McQuay H. Meta-analytic comparison of prophylactic antiemetic efficacy for postoperative nausea and vomiting: propofol anaesthesia vs omitting nitrous oxide vs total i.v. anaesthesia with propofol. *British Journal of Anaesthesia* 1997; **78**: 256–259.
42. Divatia JV, Vaidya JS, Badwe RA Omission of nitrous oxide during anesthesia reduces the incidence of postoperative nausea and vomiting. A meta-analysis. *Anesthesiology* 1996; **85** 1055–1062.
43. Luttropp HH, Romner B, Perhag L, Eskilsson J, Fredriksen S, Werner O. Left ventricular performance and cerebral haemodynamics during xenon anaesthesia. A transoesophageal echocardiography and transcranial Doppler sonography study. *Anaesthesia* 1993, **48**: 1045–1049.
44. Marx T, Froeba G, Wagner D, Baeder S, Goertz A, Georgieff M. Effects on haemodynamics and catecholamine release of xenon anaesthesia compared with total i.v. anaesthesia in the pig. *British Journal of Anaesthesia* 1997; **78**: 326–327

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Comparison of the effects of halothane, isoflurane and methoxyflurane on the electroencephalogram of the horse

C. B. Johnson and P. M. Taylor

Summary

We have investigated in eight ponies the effects of three different end-tidal concentrations of halothane, isoflurane and methoxyflurane on median (F50) and 95% spectral edge (F95) frequencies of the EEG and the second differential (DD) of the middle latency auditory evoked potential (MLAEP). The three concentrations of each agent were chosen to represent approximately the minimum alveolar concentration (MAC), 1.25 MAC and 1.5 MAC for each agent. During halothane anaesthesia, F95 decreased progressively as halothane concentration increased, from mean 13.9 (SD 2.6) at 0.8% to 11.9 (1.1) at 1.2%. DD was lower during anaesthesia with the highest concentration (21 (6.5)) compared with the lowest (27.6 (11.4)). There were no significant changes in F50. During isoflurane anaesthesia, there was a small, but significant increase in F95 between the intermediate and highest concentrations (10.2 (1.5) to 10.8 (1.6)). There were no changes in F50 and DD. Values of F95, F50 and DD at all isoflurane concentrations were similar to those of halothane at the highest concentration. During methoxyflurane anaesthesia, F95 and F50 decreased progressively as methoxyflurane concentration was increased, from 21.3 (0.7) and 6.5 (1), respectively, at 0.26%, to 20.1 (0.6) and 5.6 (0.8), respectively, at 0.39%. DD was lower during anaesthesia with the highest concentration of methoxyflurane (25.7 (7.8)) compared with the lowest (39.7 (20.6)). Values of F95, F50 and DD at all methoxyflurane concentrations were higher than those seen with halothane at the lowest concentration. The different relative positions of the dose–response curves for EEG and MLAEP changes compared with antinociception (MAC) changes suggest differences in the mechanisms of action of these three agents. These differences may explain the incomplete adherence to the Meyer–Overton rule. (*Br. J. Anaesth.* 1998; **81**: 748–753).

Keywords: anaesthetic volatile, halothane; anaesthetic volatile, isoflurane; anaesthetic volatile, methoxyflurane; monitoring, electroencephalography; horse

In humans, the effects of inhalation agents on the EEG have been studied under various conditions. In surgical patients, frequency spectra obtained under adequate and increased end-tidal isoflurane concentrations have been graded.[1] The progressive changes in frequency spectra were then colour-coded to produce a colour index of depth of anaesthesia. Graded changes in power spectra with increasing arterial halothane concentrations have also been found in infants undergoing facial surgery.[2] Despite these changes, the EEG recorded before the start of surgery could not be used to predict movement in response to surgical stimulation.[3] This confirmed similar results in the rat.[4]

The effects of 0.5%, 1% and 1.5% halothane and 0.5%, 1%, 1.5% and 2% isoflurane were compared as part of a balanced anaesthetic technique on the EEG.[5] It was found that most of the change in EEG variables with isoflurane occurred at concentrations less than MAC. In contrast, halothane produced progressive EEG changes with increasing PE_{Hal} at values greater than MAC. The values found for isoflurane from MAC onwards were similar to each other in magnitude and to those found with halothane at 1.5%.

In the horse, the EEG effects of isoflurane, halothane, methoxyflurane and enflurane have been compared.[6] A gradual change from control high frequency–low amplitude patterns to high amplitude slow waves was found with halothane and methoxyflurane. In contrast, enflurane and isoflurane anaesthesia were characterized by slow wave activity throughout with periods of burst suppression, occurring with increased concentrations. These effects were not fully described in terms of quantitative EEG variables. The effects of halothane in anaesthetized horses without surgery have been demonstrated quantitatively after induction of anaesthesia using xylazine–ketamine[7] and thiopental.[8] Both studies found progressive changes in derived EEG variables with increasing PE_{Hal}. The EEG effects of halothane have been compared with those of isoflurane in horses undergoing orthopaedic surgery.[9] Similar EEG values were found in both groups, however, more changes were seen in response to surgery with halothane than with isoflurane.

In humans, the middle latency auditory evoked potential (MLAEP) has been found to change in a dose-related manner with inhalation anaesthetic agents.[10–12] Although most of the depression in the MLAEP occurs at sub-MAC anaesthetic concentrations, graded changes have been described for concentrations of up to 2 MAC of halothane and

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Table 1 End-tidal concentrations of inhalation agents used at the three steady states studied

Approximate MAC multiple	Halothane	Isoflurane	Methoxyflurane
1	0.8%	1.2%	0.26%
1.25	1.0%	1.5%	0.32%
1.5	1.2%	1.8%	0.39%

enflurane.[10 12] In contrast, depression of the MLAEP with isoflurane appears to be complete by 1 MAC.[11] There are no data available on the effects of anaesthesia on the equine MLAEP.

The aim of this study was to compare the quantitative effects of isoflurane, halothane and methoxyflurane on the equine EEG at concentrations greater than MAC, without surgical stimulation. This would provide a direct comparison of the effects of each agent on three different measures of CNS function and also provide comparative information allowing the EEG effects of the three agents to be compared with each other. Halothane and isoflurane were chosen as they are the two main agents used in clinical equine anaesthesia. Methoxyflurane was used as it is analgesic at sub-MAC concentrations[13] and so may have quantitatively different effects from the other two agents.

Materials and methods

We studied eight pony geldings, aged 5–10 yr (mean 7 yr), weighing 270–325 kg (mean 305 kg). The ponies all had the right carotid artery raised surgically to a subcutaneous position. The study was carried out in accordance with the Animals (Scientific Procedures) Act, 1986 (Home Office Licence 80/666).

After placement of a 14-gauge cannula in the left jugular vein, anaesthesia was induced on three occasions by i.v. injection of thiopental 3 g. Additional thiopental was given as required in 0.5- or 1-g increments to allow tracheal intubation, resulting in a mean dose of 12 (SD 2) mg kg^{-1}. The ponies were placed in the left lateral recumbent position. Anaesthesia was maintained by inhalation of halothane, isoflurane or methoxyflurane from a circle breathing system (JD Medical). A 20-gauge cannula was placed in the raised carotid artery. The order in which each pony was given each anaesthetic agent was not randomized, but at least 2 weeks were left between subsequent anaesthetics in each animal.

$P\text{E}'_{\text{CO}_2}$ was monitored using an infrared monitor (Supermon 7210, Kontron Instruments) and end-tidal halothane ($P\text{E}_{\text{Hal}}$), isoflurane ($P\text{E}_{\text{Iso}}$) and methoxyflurane ($P\text{E}_{\text{Meth}}$) concentrations were monitored using a Piezo-electric anaesthetic agent monitor (Agent Monitor 7860, Kontron Instruments). As the agent monitor was not able to measure methoxyflurane concentration directly, it was set to measure halothane and the sensitivity to methoxyflurane measured before and immediately after each experiment using a calibrated methoxyflurane vaporizer set to deliver 1% methoxyflurane. The vaporizer was calibrated at a range of flows and settings using a Hillgram–Watt refractometer before the start of the study. Gas samples were obtained from the level of the end of the tracheal tube adjacent to the breathing system. Respiration was controlled by IPPV using the ventilator incorporated in the large animal circle system (modified Bird 7). Peak inspiratory pressure was set at 20–25 cm H_2O.

During anaesthesia, ECG and arterial pressure (AP) were monitored using the Supermon. The ECG was recorded using transdermal stainless steel needle electrodes with standard lead configuration. AP was recorded using a disposable pressure transducer (TXX-R, Ohmeda) connected to the carotid artery cannula. ECG and AP were recorded on a chart recorder (Lectromed two channel recorder).

Exhaled anaesthetic concentrations were maintained at the required setting for each epoch of data collection by alteration of the vaporizer setting. $P\text{E}'_{\text{CO}_2}$ was maintained at 5.3–5.9 kPa by alteration of ventilatory frequency. Experimental studies were started 60 min after induction of anaesthesia.

On each occasion three 15-min data epochs were recorded at equivalent $P\text{E}_{\text{Hal}}$, $P\text{E}_{\text{Iso}}$ in terms of multiples of the MAC of each agent. Concentrations of each agent used together with their multiple of MAC are shown in table 1. MAC values of 0.88, 1.31 and 0.3 were used for halothane,[14] isoflurane[14] and methoxyflurane (Steffey, personal communication), respectively. The end-tidal concentration was adjusted for each epoch using the vaporizer and was held at a steady state for 10 min before data collection. Data were always collected in the order 1 MAC, followed by 1.25 MAC, followed by 1.5 MAC. An arterial blood sample was obtained anaerobically via the cannula in the carotid artery for analysis of blood pH, $P\text{O}_2$ and $P\text{CO}_2$ immediately before the start and after the end of each data epoch. The average of the two values was calculated and taken as the value during that data epoch.

Throughout the experiments, the EEG was recorded using a dedicated preamplifier with an inbuilt auditory stimulus generator (Alert, Medelec). Three transcutaneous stainless steel needle electrodes were positioned in a similar manner to that used in conscious ponies.[15] The active (non-inverting) electrode was placed in the midline over the suture of the parietal bones 2–3 cm rostral to the convergence of the temporalis muscles. The reference (inverting) electrode was placed over the bony prominence of the right zygomatic arch. The ground electrode was placed 5–6 cm caudal to the poll, 5–6 cm to the right of the midline. This positioning of electrodes gave reliable EEG recordings and a well defined MLAEP. Electrodes were positioned as soon as practicable after induction of anaesthesia and were not moved or disconnected for the duration of the study. Data were recorded to a personal computer (450L, Dell) via a digital signal processing card (DSP with sub-board and 64k RAM, Loughborough Sound Instruments). Data recording software was used which was developed specifically for this hardware combination (Auditory Evoked Response Program, Chris Jordan, Northwick Park Hospital).

EEG data were recorded with a sample rate of 1 kHz and a passband of 0.5–400 Hz. Data were divided into 2-s epochs and artefact rejection was performed manually off-line by inspection of the raw data. Any epochs containing artefact were rejected before further processing. Data blocks containing

Table 2 Arterial pH, $P\text{CO}_2$, $P\text{O}_2$ and mean arterial pressure (AP) for each agent concentration during EEG recording (mean (SD)). $^*P<0.05$ denote values significantly different from each other

Agent	Concentration	pH	$P\text{CO}_2$	$P\text{O}_2$	Mean AP
Halothane	0 8%	7.325 (0.081)	6.1 (1)	36.1 (14.1)	10.9 (1.3)
	1.0%	7.329 (0.104)	6 1 (1.2)	39.2 (15.8)	11.7 (1.3)
	1.2%	7.297 (0.138)	6.7 (1.9)	32.2 (16.8)	11.8 (1.5)
Isoflurane	1.2%	7.387 (0.029)	5.3 (0.2)	42.6 (12.5)	10.3 (1.2)
	1.5%	7.39 (0.037)*	5.4 (0.4)*	46.6 (16.4)	10.5 (1.3)
	1.8%	7.405 (0.036)*	5.1 (0.5)*	46.8 (18.5)	10.5 (1.1)
Methoxyflurane	0.26%	7.382 (0.02)	5.9 (0.6)	48.9 (7.3)	16.1 (1.9)*
	0.32%	7.375 (0.021)	5.9 (0.5)	48.3 (7.3)	12.8 (2.6)
	0.39%	7.382 (0.034)	5.7 (0.6)	45 6 (8.4)	12.1 (1.9)*

overscale or underscale values were rejected as were blocks containing burst suppression, specific muscular activity such as nystagmus or other identifiable EMG.

Throughout the period of data recording, a broadband binaural click stimulus was presented to the ponies. This stimulus was generated by the EEG recording system and was delivered by audio ear pieces (FEN20, Ross Audio) placed in the external auditory meatii. On each occasion the ear pieces were inserted in a similar manner and to a similar depth. No animals showed signs of auditory canal pathology or excessive wax build up at any time during the study. The auditory stimulus had a pulse width of 0.4 ms and was delivered at a rate of 6.1224 Hz.

The raw EEG was analysed using specialized software (Spectral Analysis Program, Chris Jordan Northwick Park Hospital). Fast Fourier transformation was performed on each 2-s block of data using a 10% raised cosine window function. The resultant frequency histograms were analysed further to produce a median frequency (F50) and 95% spectral edge frequency (F95). F50 and F95 were averaged over 30 consecutive blocks to give a single value for each minute of recording.

MLAEP was derived by averaging of the EEG signal. The 100 ms of EEG after each click stimulus were averaged over 512 consecutive artefact-free sweeps. A 100-Hz low pass filter was applied to the data before calculation of the second differential to remove any contribution of higher frequencies to the calculation. The second differential (DD) of the area of the MLAEP between 30 and 90 ms after the stimulus was estimated by the software using the following function:

$$y(n)=x(n+d)+x(n-d)-2\times x(n)$$

where $x(n)$=nth sample value, d=sample interval used in the calculation and $y(n)$=second differential estimate for sample n.

The second differential estimate was calculated for each sample point over the period from 30 to 90 ms post-stimulus. These estimates were summated to give an index which was scaled so that a typical human MLAEP would give a value of ≥100 in an awake patient and 10–15 in a deeply anaesthetized patient.[16]

In order to standardize the MLAEP data, DD derived from each waveform were assigned to the nearest whole number of minutes after the start of the experiment to the last sweep which was included in the signal average.

F95, F50 and DD for all data epochs at each agent concentration were compared using analysis of variance with Dunnett's *post hoc* test[17] where statistically significant differences were found. pH, $P\text{O}_2$ and $P\text{CO}_2$ were compared for all animals in a similar manner.

Results

There were no data after isoflurane anaesthesia for one pony as this experiment was abandoned because of repeated violent movements at both 1.2% and 1.5% isoflurane. EEG data from one pony during halothane anaesthesia were not included as they were found to be contaminated by high frequency (50 Hz) artefacts. There were no arterial blood-gas data after halothane anaesthesia for two of the ponies because of a malfunction of the blood-gas analyser.

There were no significant differences in pH, $P\text{O}_2$, $P\text{CO}_2$ or mean AP recorded during administration of the three concentrations of halothane. There were statistically significant reductions in $P\text{CO}_2$ and increases in pH between 1.5% and 1.8% end-tidal isoflurane. There was a statistically significant decrease in AP between 0.26% and 0.39% end-tidal methoxyflurane. All blood-gas data are shown in table 2.

Values for F95, F50 and DD with halothane are shown for all animals in table 3. Values for individual animals are illustrated in figure 1. When all animals were considered together, there was a progressive reduction in F95 which was statistically significant for all three $P\text{E}_{\text{Hal}}$. There were no significant changes in F50 with increasing $P\text{E}_{\text{Hal}}$. There was a statistically significant reduction in DD between 0.8% and 1.2%$P\text{E}_{\text{Hal}}$.

Values for F95, F50 and DD with isoflurane are shown for all animals in table 4. Values for individual animals are illustrated in figure 2. When all animals were considered together, there was a significant increase in F95 between 1.5% and 1.8% $P\text{E}_{\text{Iso}}$. There

Table 3 Change in F95, F50 and DD with $P\text{E}_{\text{Hal}}$ (mean (SD)). $^*P<0.05$ denotes values significantly different from each other; $^\dagger P<0.05$ denotes values significantly different from all others in group

	$P\text{E}_{\text{Hal}}$		
	0.8%	1.0%	1.2%
F95	13.9 (2.6)†	13 (1.6)†	11.9 (1.1)†
F50	3 (0 9)	3 1 (0.5)	2.8 (0.5)
DD	27 6 (11.4)*	24.8 (10.1)	21 (6.5)*

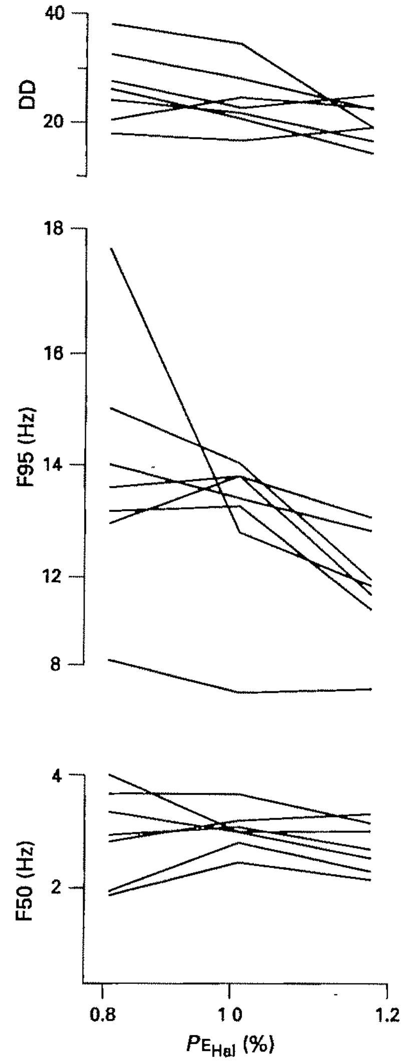

Figure 1 F95, F50 and DD values for $P\mathrm{E}_{\mathrm{Hal}}$ in individual animals (see table 3 for significant differences between values).

were no significant differences in F50 or DD. Values of F95, F50 and DD with isoflurane at all $P\mathrm{E}_{\mathrm{Iso}}$ were similar to those seen with halothane at 1.2%.

Values for F95, F50 and DD with methoxyflurane are shown for all animals in table 5. Values for individual animals are illustrated in figure 3. When all animals were considered together, there was a significant decrease in F95 and F50 between 0.26% and 0.39% $P\mathrm{E}_{\mathrm{Meth}}$. DD at 0.39% was significantly less than that at 0.26%. Values for F95, F50 and DD seen with methoxyflurane at all $P\mathrm{E}_{\mathrm{Meth}}$ were greater than those seen with halothane at 0.8%.

Burst suppression was a feature of the EEG during isoflurane anaesthesia. There was an increasing incidence with increasing $P\mathrm{E}_{\mathrm{Iso}}$. Burst suppression was not seen during halothane or methoxyflurane anaesthesia.

Table 4 Change in F95, F50 and DD with $P\mathrm{E}_{\mathrm{Iso}}$ (mean (SD)). $^{*}P<0.05$ denotes values significantly different from each other

	$P\mathrm{E}_{\mathrm{Iso}}$		
	1.2%	1.5%	1.8%
F95	10 (1.7)	10.2 (1.5)*	10.8 (1.6)*
F50	2.4 (0.4)	2.4 (0.3)	2.4 (0.5)
DD	23.3 (6.8)	23.2 (6.8)	22.7 (9.2)

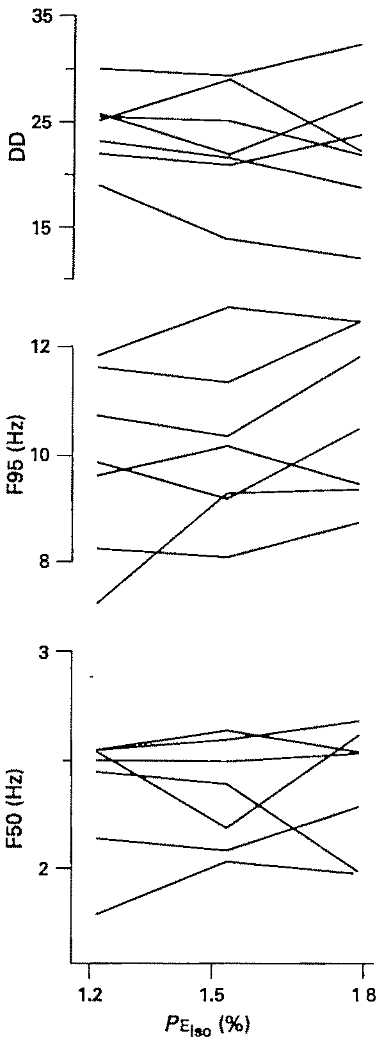

Figure 2 F95, F50 and DD values for $P\mathrm{E}_{\mathrm{Iso}}$ in individual animals (see table 4 for significant differences between values).

Discussion

We have shown that the EEG effects of the three inhalation agents halothane, isoflurane and methoxyflurane were quantitatively different from each other compared with the MAC of these agents. Within the concentration window studied, halothane produced a progressive reduction in F95, F50 and DD while the values for isoflurane were all at one extreme of the halothane curve and the values for methoxyflurane all at the other extreme. As a progressive increase in the incidence of burst suppression was seen with increasing $P\mathrm{E}_{\mathrm{Iso}}$, the values for isoflurane may represent maximal depression of F95, F50 and DD.

Data were collected in the order 1 MAC, followed by 1.25 MAC, followed by 1.5 MAC. In a previous

Table 5 Change in F95, F50 and DD with $P\mathrm{E}_{\mathrm{Meth}}$ (mean (SD)). $^{*}P<0.05$ denotes values significantly different from each other; $^{\dagger}P<0.05$ denotes values significantly different from all others in group

	$P\mathrm{E}_{\mathrm{Meth}}$		
	0.26%	0.32%	0.39%
F95	21.3 (0.7)†	20.6 (0.9)†	20.1 (0.6)†
F50	6.5 (1)†	6.1 (1)†	5.6 (0.8)†
DD	39.7 (20.6)*	31.7 (18.6)	25.7 (7.8)*

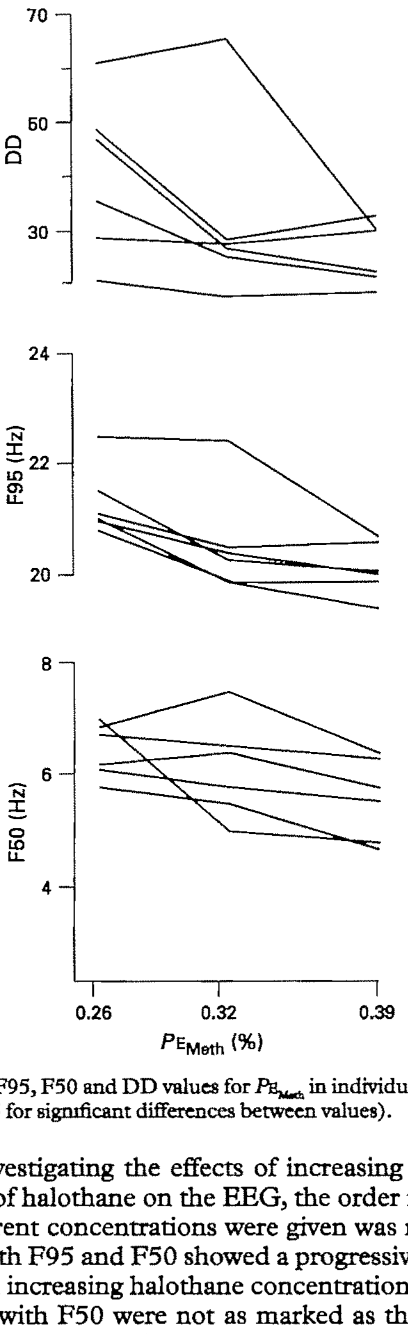

Figure 3 F95, F50 and DD values for $P\text{E}_{\text{Meth}}$ in individual animals (see table 5 for significant differences between values).

study investigating the effects of increasing concentrations of halothane on the EEG, the order in which the different concentrations were given was randomized.[8] Both F95 and F50 showed a progressive reduction with increasing halothane concentration, but the changes with F50 were not as marked as those with F95. More recently, it was suggested that F50 may respond to changes in anaesthetic concentration in a sluggish manner (D. Sapsford, personal communication). Consequently, the order of anaesthetic agent concentrations in this study was not altered between animals in an attempt to standardize this possible source of error. The similarity in the halothane results between this and the previous study[8] suggest that a sluggish response in F50 did not contribute to the results in either case.

pH and $P\text{CO}_2$ changes seen with isoflurane, and arterial pressure changes seen with methoxyflurane were small and all values were within normal limits for anaesthetized horses.[18] It is unlikely that changes of such a small magnitude would have any direct effect on the EEG variables studied.

Methoxyflurane has been demonstrated to have analgesic effects at sub-MAC concentrations.[13] In contrast, isoflurane has been shown to have no analgesic effect when given to human volunteers at subanaesthetic concentrations.[19] These differences made it desirable to include methoxyflurane in this study despite the problems encountered using this agent in the horse.[20] It was not possible to obtain $P\text{E}_{\text{Meth}}$ values higher than 0.39% and so this value was chosen together with a value less than MAC (0.26%) and an intermediate one (0.32%). These values do not directly correspond to those of halothane and isoflurane in terms of multiples of MAC. However, the quantitative differences between methoxyflurane and the other agents are too great to be explained by this alone.

The progressive decrease in F95 and DD with increasing concentrations of halothane were similar to previous findings.[5 6 8] The lack of change with isoflurane and methoxyflurane and the progressive appearance of periods of burst suppression with isoflurane were also similar.[5 6] As the EEG variables for isoflurane at all three $P\text{E}_{\text{Iso}}$ were similar to those for halothane at 1.2%, it is probable that the slope of the isoflurane dose–response curve for CNS depression occurs at a lower concentration in terms of multiples of MAC than that for halothane. Similarly, the EEG variables for methoxyflurane at all three $P\text{E}_{\text{Meth}}$ demonstrated less CNS depression than 0.8% halothane, suggesting that CNS depression occurs at higher concentrations in terms of multiples of MAC with methoxyflurane than either isoflurane or halothane. The difference in the relative positions of the dose–response curves for CNS depression and antinociception with halothane and isoflurane would explain the finding in the horse that the CNS was more responsive during surgery with halothane anaesthesia than isoflurane anaesthesia.[9]

The MAC of an anaesthetic agent is related to the ability of that agent to prevent response to a noxious stimulus. This is a measure of the antinociceptive potential of the anaesthetic agent. The degree of depression of the EEG variables investigated is incomplete at 1 MAC of halothane whereas with isoflurane, depression of these variables is complete by 1 MAC. The EEG variables did not appear to be completely depressed at any of the three methoxyflurane concentrations. In terms of multiples of MAC, there appears to be a spectrum of potency for CNS depression from methoxyflurane (least potent) through halothane to isoflurane. This suggests that methoxyflurane is more antinociceptive than isoflurane as response to a standard nociceptive stimulus is prevented by a concentration of methoxyflurane which induces less CNS depression than the required concentration of isoflurane. Halothane would appear to have an intermediate antinociceptive effect.

Traditionally, the inhalation agents have been the anaesthetic agents to which others have been compared. The concept of depth of anaesthesia which led to the classic signs and stages of anaesthesia[21] was developed from experience with ether and modified as other inhalation agents appeared. The inhalation agents are all volatile compounds with low molecular weight. Because of the Meyer–Overton theory[22 23] which links potency to fat solubility, it has been suggested that they have a similar site of action within a lipophilic biophase. This, together with the concept of pressure reversal, has led to the belief that general anaesthesia with the inhalation agents is a result of a physical effect in the cell membrane rather than a receptor-mediated effect and as such affects all cells in the body. This would lead to a global effect on the CNS producing a generalized depression of function rather than specific, pharmacologically localized effects.[24]

These data appear to question the usefulness of comparing effects of anaesthetic agents other than that of antinociception in terms of multiples of MAC. If the different effects of inhalation anaesthetic agents occur at different concentrations relative to each other, there must be pharmacologically localized kinetic or dynamic differences between them. Effects of inhalation anaesthetic agents at differing sites or even receptors may explain the incomplete adherence of these agents to the Meyer–Overton rule.

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References

1. Thomsen CE, Christensen KN, Rosenfalck A. Computerised monitoring of depth of anaesthesia with isoflurane. *British Journal of Anaesthesia* 1989; **63**: 36–43.
2 Sugiyama K, Joh S, Hirota Y, Kiyomitsu Y, Niwa H, Matsuura H. Relationship between changes in power spectra of electroencephalograms and arterial halothane concentration in infants. *Acta Anaesthesiologica Scandinavia* 1989; **33**: 670–675.
3. Dwyer RC, Rampil IJ, Eger EI, Bennett HL. The electroencephalogram does not predict depth of isoflurane anesthesia *Anesthesiology* 1994; **81**: 403–409.
4. Rampil IJ, Laster MJ. No correlation between quantitative electroencephalographic measurements and movement response to noxious stimuli during isoflurane anesthesia in rats. *Anesthesiology* 1992; **77**. 920–925.
5 Lloyd-Thomas AR, Cole PV, Prior PF. Quantitative EEG and BAE potentials. comparison of isoflurane with halothane using the cerebral function monitor. *British Journal of Anaesthesia* 1990, **65**. 306–312.
6. Auer JA, Amend JF, Garner HE, Hutcheson DP, Salem CA. Electroencephalographic responses during volatile anaesthesia in domestic ponies: a comparative study of isoflurane, methoxyflurane and halothane. *Electroencephalographic Responses* 1979; **3**· 130–134
7 Otto K, Short CE. Electroencephalographic power spectrum analysis as a monitor of anaesthetic depth in horses. *Veterinary Surgery* 1991; **5**: 362–371
8. Johnson CB, Young SS, Taylor PM. Analysis of the frequency spectrum of the equine electroencephalogram during halothane anaesthesia. *Research in Veterinary Science* 1994; **56**· 373–378.
9. Ekström PM, Short CE, Geimer TR. Electroencephalography of detomidine–ketamine–halothane and detomidine–ketamine–isoflurane anaesthetized horses during orthopaedic surgery: a comparison. *Veterinary Surgery* 1993; **22**· 414–418.
10. Thornton C, Heneghan CPH, James MFM, Jones JG. The effects of halothane and enflurane with controlled ventilation on the auditory evoked potentials *British Journal of Anaesthesia* 1984; **56**: 315–323.
11. Schwender D. Wachheit während narkose. Wissenschaftliche Verlagsabteilung Abbott GmbH, Wiesbaden, 1992.
12. Newton DEF, Thornton C, Jordan C. The auditory evoked response as a monitor of anaesthetic depth In. Sebel PS, Bonke B, Winograd E, eds. *Memory and Awareness in Anesthesia*. New Jersey: Prentice Hall, 1993; 274–280
13. Siker ES, Wolfson B, Ciccarelli HE, Telan RA Effect of subanesthetic concentrations of halothane and methoxyflurane on pain threshold in conscious volunteers. *Anesthesiology* 1967, **28**: 337–342
14 Steffey EP, Howland D, Giri S, Eger EI. Enflurane, halothane and isoflurane potency in horses *American Journal of Veterinary Research* 1977; **38**· 1037–1039
15. Mayhew IG, Washbourne JR A method of assessing auditory and brainstem function in horses *British Veterinary Journal* 1990; **146**. 509–518.
16. Jordan C. Auditory Evoked Response Program AVG manual, 1994.
17. Dunnett CW. New tables for multiple comparisons with a control. *Biometrics* 1964; **20**: 482–491.
18. Muir WW, Hubbell JAE, Skarda R. *Handbook of Veterinary Anaesthesia*. St Louis: Mosby, 1989.
19. Roth D, Petersen-Felix S, Bak P, Arendt-Nielsen L, Fischer M, Bjerring P, Zbinden AM. Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials. *British Journal of Anaesthesia* 1996; **76**: 38–42.
20. Steffey EP. Inhalation anaesthetics and gases. In: Muir WW, Hubbell JAE, eds. *Equine Anaesthesia*. St Louis: Mosby, 1991; 352–379
21. Guedel AE. *Inhalation Anesthesia*. New York· Macmillan, 1937.
22. Meyer HH Zur theorie der Alkoholnarkose I. MITT Welche eigenschaft der Anesthetica bedingt ihre Narkotische wirkung? *Archives of Experimental Pathological Pharmacology* 1899, **42**: 109–118.
23. Overton E. *Studien uber die narkose*. Jena: Verlag von Gustav Fischer, 1901.
24. Miller KW, Paton WDM, Smith EB Site of action of general anaesthetics. *Nature (London)* 1965; **206** 574–577.

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Prophylactic antiemetic therapy with a combination of granisetron and dexamethasone in patients undergoing middle ear surgery

Y. FUJII, H. TOYOOKA AND H. TANAKA

Summary

We have compared the efficacy of granisetron in combination with dexamethasone with each drug alone in the prevention of postoperative nausea and vomiting (PONV) after middle ear surgery. In a randomized, double-blind study, 120 patients (85 females) received granisetron 3 mg, dexamethasone 8 mg or granisetron 3 mg with dexamethasone 8 mg i.v. (n=40 in each group), immediately before induction of anaesthesia. A standardized general anaesthetic technique was used. A complete response, defined as no PONV and no need for another rescue antiemetic during the first 3 h after anaesthesia, was recorded in 83%, 50% and 98% of patients who had received granisetron, dexamethasone and granisetron–dexamethasone, respectively. The corresponding incidences during the next 21 h after anaesthesia were 80%, 55% and 98% (P<0.05; overall Fisher's exact probability test). In summary, prophylactic use of combined granisetron and dexamethasone was more effective than each antiemetic alone for the prevention of PONV after middle ear surgery. (*Br. J. Anaesth.* 1998; **81**: 754–756).

Keywords. vomiting, nausea; vomiting, antiemetics, granisetron; vomiting, antiemetics, dexamethasone; surgery, otolaryngological

Postoperative nausea and vomiting (PONV) occur frequently after middle ear surgery, with incidences as high as 80% when no prophylactic antiemetic is given.[1-3] We have demonstrated recently that granisetron, a selective 5-hydroxytryptamine type 3 (5-HT$_3$) receptor antagonist, reduces the incidence of PONV in patients undergoing general anaesthesia for middle ear surgery.[4] However, this antiemetic cannot entirely control PONV after middle ear surgery. Dexamethasone has been used as an antiemetic in patients receiving chemotherapy, with limited side effects,[5] and has also been reported to decrease chemotherapy-induced emesis when added to an antiemetic regimen.[6] In this study, we have compared the efficacy of granisetron with dexamethasone with each antiemetic alone for the prevention of PONV in patients undergoing middle ear surgery.

Patients and methods

After obtaining approval from the Institutional Review Board and informed consent, we studied 120 ASA I patients (85 females), aged 25–60 yr, undergoing middle ear surgery (tympanoplasty or mastoidectomy). Patients with gastrointestinal diseases, those who had received any antiemetic medication within 24 h before surgery, and those who were pregnant or menstruating were excluded.

Patients were allocated randomly to receive one of three treatment regimens (n=40 each): granisetron 3 mg, dexamethasone 8 mg or granisetron 3 mg with dexamethasone 8 mg. The drugs were administered i.v. immediately before induction of anaesthesia. A randomization list was prepared by a random number function in a computer spreadsheet and identical syringes containing each drug were prepared by personnel not involved in the study.

Patients received no preanaesthetic medication. Anaesthesia was induced with thiopental 5 mg kg^{-1} and fentanyl 2 μg kg^{-1} i.v., and vecuronium 0.2 mg kg^{-1} i.v. was used to facilitate tracheal intubation. Anaesthesia was maintained with 1.0–3.0% isoflurane (inspired concentration) and 66% nitrous oxide (which was replaced by air before closing the tympanic membrane) in oxygen. Ventilation was controlled mechanically and adjusted to maintain end-tidal carbon dioxide concentration at 4.6–5.2 kPa throughout surgery using an anaesthetic–respiratory analyser (Ultima, Datex, Helsinki, Finland). Patients were not given opioids during surgery. A nasogastric tube was inserted and suction applied to empty the stomach of air and other contents. Before tracheal extubation, the nasogastric tube was again suctioned and removed. Neuromuscular block was achieved with vecuronium and antagonized by atropine 0.02 mg kg^{-1} i.v. and neostigmine 0.04 mg kg^{-1} i.v. at the end of surgery. The trachea was extubated when the patient was awake. Rectal temperature was monitored and maintained at 37±1°C throughout surgery. If two or more episodes of vomiting occurred during the first 24 h after anaesthesia, rescue antiemetic (e.g. metoclopramide 0.2 mg kg^{-1}) was given. After operation, patients received indomethacin 50 mg rectally if they complained of moderate to severe pain.

During the first 24 h after anaesthesia (i.e. 0–3 h in the post-anaesthetic unit and 3–24 h on the ward), all episodes of PONV (nausea, retching, vomiting) were recorded every 3 h by blinded nursing staff. The nurses asked the patients if retching or vomiting had

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Table 1 Patient characteristics (mean (SD or range) or number). Combination=Granisetron with dexamethasone. No significant differences

	Granisetron (n=40)	Dexamethasone (n=40)	Combination (n=40)
Age(yr)	45(25–60)	42(25–60)	44(25–60)
Sex(F/M)	29/11	28/12	28/12
Height(cm)	158(8)	159(8)	158(7)
Weight(kg)	56(8)	56(8)	58(8)
History of motion sickness(n)	3	3	3
History of previous PONV(n)	2	2	2
Duration of operation(min)	217(40)	214(42)	218(39)
Duration of anaesthesia(min)	247(40)	243(44)	247(41)
Indomethacin used after operation (n)	22	23	22
Types of operation performed(n)			
Tympanoplasty	30	30	29
Mastoidectomy	10	10	11

occurred and if they felt nauseated, with only two possible answers (yes/no). Nausea was defined as the unpleasant sensation associated with awareness of the urge to vomit; retching was defined as laboured, spasmodic, rhythmic contraction of the respiratory muscles without expulsion of gastric contents; and vomiting was defined as the forceful expulsion of gastric contents from the mouth.[7] A complete response was defined as no PONV and no need for rescue antiemetic medication. Details of adverse events throughout the study were recorded by follow-up nurses who asked patients general questions and also recorded spontaneous complaints.

Statistical analysis was by ANOVA with Bonferroni correction for multiple comparison, chi-square test or Fisher's exact probability test, as appropriate (Stat View 4.0; Macintosh). $P<0.05$ was considered significant. All values are expressed as mean (SD, range) or number (%). We set a=0.05 and β=0.2, and used a large magnitude of effects (effective size 0.8) to estimate a sufficient sample size. The analysis showed that 40 patients per treatment group would be sufficient.

Results

Patient characteristics and surgical procedures were similar in each group (table 1).

A complete response during the first 3 h (0–3 h) after anaesthesia was recorded in 83%, 50% and 98% of patients who had received granisetron, dexamethasone and granisetron–dexamethasone, respectively. The incidences during the next 21 h (3–24 h) after anaesthesia were 80%, 55% and 98%, respectively. Thus a complete response within the first 24 h after anaesthesia was achieved significantly more often in patients who had received a combination of granisetron and dexamethasone than in those who had received granisetron or dexamethasone alone (table 2).

The most frequently reported adverse events were headache and dizziness, but there were no differences between groups (table 3).

Discussion

Postoperative nausea and vomiting (PONV) are among the most common complications after anaesthesia and surgery, with a relatively high incidence after middle ear surgery (tympanoplasty or mastoidectomy).[1–3] Our previous study found that the incidence of PONV was as high as 60% in patients undergoing general anaesthesia for middle ear surgery.[4 8] This incidence may justify the use of prophylactic antiemetics for the prevention of PONV after middle ear surgery.

The aetiology of PONV after middle ear surgery performed under general anaesthesia is not known, but is probably multifactorial.[7] Several factors, including age, sex, obesity, history of motion sickness and/or previous PONV, menstruation, surgical procedure, anaesthetic technique and postoperative pain are considered to affect the incidence of PONV. In this study, however, these factors were well balanced between groups. An increased middle ear pressure by nitrous oxide is also one of the surgical factors contributing to PONV.[5] As middle ear pressure was measured in this study, no pressure was generated in the middle ear from diffusion of nitrous oxide, which was replaced by air before closing the tympanic membrane. Therefore, the difference in complete response between the groups may be attributed to differences in the antiemetic drugs administered.

We have demonstrated recently that granisetron 40 μg kg^{-1} reduced the incidence of PONV in patients undergoing middle ear surgery,[3] and also that the efficacy of granisetron 40 μg kg^{-1} was similar to that of granisetron 100 μg kg^{-1} for the prevention of PONV in this population.[8] The dose chosen for this study was 3 mg (approximately 55 μg kg^{-1}). It has been reported that dexamethasone 8 mg decreased chemotherapy-induced emesis when added to an antiemetic regimen.[6] Therefore, in this study, the same dose of dexamethasone was added to granisetron 3 mg.

The precise mechanism of action of granisetron–dexamethasone in the augmentation of a complete response remains unclear, but granisetron antagonizes 5-HT$_3$ receptors in sites associated with antiemetic activity[9] and dexamethasone may also inhibit stimulation of 5-HT$_3$ receptors.[10] Dexamethasone did not increase the incidence of adverse events when added to granisetron.

We conclude that prophylactic therapy with a combination of granisetron and dexamethasone was more effective than each antiemetic alone for the prevention of PONV after middle ear surgery. This suggests that dexamethasone may be used as a

Table 2 Number (%) of patients with a complete response (no PONV, no rescue) and incidence of nausea, retching, vomiting and rescue antiemetic during the first 3 h (0–3 h) and the next 21 h (3–21 h) after anaesthesia. Combination=granisetron with dexamethasone; P_1 values=granisetron vs dexamethasone; P_2 values=granisetron vs combination; and P_3 values=dexamethasone vs combination

	Granisetron (*n*=40)	Dexamethasone (*n*=40)	Combination (*n*=40)	P_1	P_2	P_3
0–3 h after anaesthesia						
Complete response (no PONV, no rescue)	33(83%)	20(50%)	39(98%)	0.002	0.028	0.001
Nausea	4(10%)	10(25%)	1(3%)	0.069	0.179	0.003
Retching	1(3%)	2(5%)	0(0%)	0.5	0.5	0.247
Vomiting	3(8%)	10(25%)	1(3%)	0.033	0.308	0.003
Rescue	0(0%)	5(13%)	0(0%)	0.027	1.0	0.027
3–24 h after anaesthesia						
Complete response (no PONV, no rescue)	32(80%)	22(55%)	39(98%)	0.015	0.014	0.001
Nausea	4(10%)	9(23%)	1(3%)	0.112	0.179	0.007
Retching	2(5%)	2(5%)	0(0%)	1.0	0.247	0.247
Vomiting	3(8%)	9(23%)	1(3%)	0.057	0.308	0.007
Rescue	0(0%)	5(13%)	0(0%)	0.027	1.0	0.027

Table 3 Adverse events (number (%)). No significant differences

	Granisetron (*n*=40)	Dexamethasone (*n*=40)	Combination (*n*=40)
0-3 h after anaesthesia			
Headache	3(8%)	3(8%)	3(8%)
Dizziness	2(5%)	2(5%)	2(5%)
Others(constipation, muscle pain)	2(5%)	1(3%)	2(5%)
3-24 h after anaesthesia			
Headache	3(8%)	3(8%)	3(8%)
Dizziness	2(5%)	2(5%)	2(5%)
Others (constipation, muscle pain)	1(3%)	1(3%)	1(3%)

component of combined prophylaxis for the control of PONV in patients undergoing other surgical procedures.

References

1. Honkavaara P, Saarinvaara L, Klemola U-K. Prevention of nausea and vomiting with transdermal hyoscine in adults after middle ear surgery during general anaesthesia. *British Journal of Anaesthesia* 1994; 73: 763–766.
2. Honkavaara P. Effect of ondansetron on nausea and vomiting after middle ear surgery during general anaesthesia. *British Journal of Anaesthesia* 1996; 76: 316–318.
3. Reinhart DJ, Klein KW, Schroff E. Transdermal scopolamine for the reduction of postoperative nausea in outpatient ear surgery: a double-blind, randomized study. *Anesthesia and Analgesia* 1994; 79: 281–284.
4. Fujii Y, Toyooka H, Tanaka H. Granisetron reduces the incidence of nausea and vomiting following middle ear surgery. *British Journal of Anaesthesia* 1997; 79: 539–540.
5. Aapro MS, Alberts DS. Dexamethasone as an antiemetic in patients treated with cisplatin. *New England Journal of Medicine* 1981; 305: 520.
6. Smith DB, Newlands ES, Rustin GJS, Begent RHJ, Howells N, McQuade B, Bagshawe KD. Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin containing chemotherapy. *Lancet* 1991; 338: 487–490.
7. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology* 1992; 77: 162–184.
8. Fujii Y, Toyooka H, Tanaka H. Granisetron in the prevention of nausea and vomiting following middle ear surgery: a dose ranging study. *British Journal of Anaesthesia* 1998; 81: (in press).
9. Carmichael J, Cantwell BM, Edwards CM, Zussmann BD, Thompson S, Rapeport WG, Harris AL. A pharmacokinetic study of granisetron (BRL 43694A), a selective 5-HT_3 receptor antagonist: correlation with anti-emetic response. *Cancer Chemotherapy and Pharmacology* 1989; 24: 45–49.
10. Aapro BMJ, Plezia PM, Alberts DS, Graham V, Jones SE, Surwit EA, Moon TE. Double-blind crossover study of the antiemetic efficacy of high-dose dexamethasone versus high-dose metoclopramide. *Journal of Clinical Oncology* 1984; 2: 466–471.

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Neostigmine with glycopyrrolate does not increase the incidence or severity of postoperative nausea and vomiting in outpatients undergoing gynaecological laparoscopy

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Summary

We studied 100 healthy women undergoing outpatient gynaecological laparoscopy in a randomized, double-blind and placebo-controlled study to evaluate the effect of neostigmine on postoperative nausea and vomiting (PONV). After induction of anaesthesia with propofol, anaesthesia was maintained with sevoflurane and 66% nitrous oxide in oxygen. Mivacurium was used for neuromuscular block. At the end of anaesthesia, neostigmine 2.0 mg and glycopyrrolate 0.4 mg, or saline, was given i.v. The incidence of PONV was evaluated in the postanaesthesia care unit, on the ward and at home. The severity of nausea and vomiting, worst pain, antiemetic and analgesic use, times to urinary voiding and home readiness were recorded. During the first 24 h after operation, 44% of patients in the neostigmine group and 43% in the saline group did not have PONV. We conclude that neostigmine with glycopyrrolate did not increase the occurrence of PONV in this patient group. (*Br. J. Anaesth.* 1998; **81**: 757–760).

Keywords: antagonists, neuromuscular block, neostigmine; parasympathetic nervous system, glycopyrrolate; vomiting, nausea; surgery, laparoscopy

Postoperative nausea and vomiting (PONV) are common in patients undergoing gynaecological laparoscopic surgery.[1] In outpatient anaesthesia, rapid emergence and low incidence of side effects are necessary to ensure early discharge.[2] A combination of propofol and sevoflurane is usually associated with fast recovery,[3] although a high incidence of PONV still remains.

Mivacurium is a short-acting non-depolarizing neuromuscular blocking agent which is hydrolysed by plasma cholinesterase and can thus be used without reversal.[4] Recovery after a mivacurium infusion can also be accelerated by neostigmine with a dose of at least 20 μg kg^{-1}.[5] The effect of reversal drugs on PONV has been studied in inpatients,[6 7] outpatients[8 9] and children.[10] The results are controversial.

We studied patients undergoing outpatient gynaecological laparoscopic surgery, and tested the hypothesis that administration of neostigmine to patients at the end of propofol–sevoflurane–nitrous oxide anaesthesia increases PONV, compared with patients without antagonism of mivacurium block.

Patients and methods

After obtaining approval from the local Ethics Committee of Helsinki University Central Hospital and informed patient consent, we studied 100 healthy women undergoing outpatient gynaecological diagnostic or operative laparoscopy (tubal ligations excluded), in a randomized, double-blind, placebo-controlled study. Other exclusion criteria were obesity (body mass index >27 kg m^{-2}) and known allergy to ketoprofen. Calculation of sample size was based on our previous study with a similar patient population.[11]

Patients were premedicated with diazepam 5 mg orally 30–60 min before surgery. Before induction of anaesthesia, infusion of Ringer's acetate was started, and patients received glycopyrrolate 0.2 mg and fentanyl 0.1 mg i.v. Anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and mivacurium 0.2 mg kg^{-1} i.v. When needed, patients were given mivacurium either as boluses or as a continuous infusion with a syringe pump to maintain neuromuscular block (less than two twitches in the train-of-four (TOF)). Anaesthesia was maintained with 1.0–1.3 MAC of sevoflurane and 66% nitrous oxide in oxygen. Routine anaesthesia monitoring was used (AS/3, Datex, Helsinki, Finland). When heart rate or arterial pressure values, or both, increased to more than 20% of preanaesthetic values and end-tidal sevoflurane was already adjusted at 1.3 MAC, patients received a bolus dose of alfentanil 0.5 mg. After surgery, sevoflurane was discontinued before nitrous oxide. The time when nitrous oxide was discontinued was considered the end of anaesthesia. Before this, ketoprofen 100 mg i.v. was given. At the end of anaesthesia, when four twitches of TOF were visible with fade, participants were allocated randomly to the study (neostigmine) or control (saline) group (n=50 in each group). Patients in the study group were given neostigmine 2.0 mg and glycopyrrolate 0.4 mg in a volume of 6 ml. Patients in the control group received 6 ml of saline i.v.

For pain relief, when needed, patients were given fentanyl 0.05 mg i.v. or ketoprofen 100 mg as a slow i.v. infusion or rectally (maximum dose 300 mg in 24 h). Postoperative antiemetic medication was given

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for symptoms of prolonged nausea or vomiting according to a strict protocol in the postanaesthesia care unit (PACU): droperidol 0.1 mg/10 kg i.v. was given twice, followed by ondansetron 4 mg i.v. twice. For patients whose i.v. cannula was already discontinued in the ward, metoclopramide 10 mg rectally was given. Antiemetics were administered to patients on the ward according to clinical judgment.

Postoperative nausea and vomiting (PONV) were estimated as in our previous studies[12 13] on a scale of 0–3 (0=no nausea, 1=mild nausea, duration <15 min, 2=prolonged nausea >15 min, 3=retching or vomiting) at awakening and 30, 60 and 90 min after anaesthesia in the PACU. If the patient had both nausea and vomiting, she was recorded only once as having vomited. The visual analogue scale (VAS; 0–10 cm) for patient satisfaction was used on the ward and during the first 24 h at home. The worst pain in the PACU, on the ward and at home was recorded using a four-point scale (none/mild/moderate/severe). An anaesthetist interviewed the patient before discharge and gave her a questionnaire to record pain and PONV symptoms (0–3 scale) during the first 24 h at home. In the PACU, the patient was not allowed to drink, whereas on the ward she was encouraged to drink and ambulate. Home readiness was defined using standard criteria[14] such as the time after the end of anaesthesia when the patient was able to walk, take oral fluids, void and 30 min had passed after the last administration of opioid or antiemetic.

Statistical analysis was performed using the unpaired *t* test, chi-square test and the Mann–Whitney *U* test, where appropriate. Power analyses were calculated by a commonly available public domain program. For all other analyses SPSS for Windows statistical package was used. $P<0.05$ was considered significant.

Results

We recruited 100 patients (table 1), but two patients in the saline group were excluded from analysis; laparoscopy in one patient was converted to laparotomy, and collection of data for the other was incomplete. Follow-up questionnaires were returned by 86% of patients. Perioperative data are shown in table 2. Alfentanil bolus doses were administered during anaesthesia to 38% of patients in the neostigmine group and to 42% in the saline group. A drain in the peritoneal cavity was inserted in 34% and 29% of patients, respectively.

The incidence of PONV is shown in table 3. There were no differences in the incidence or severity of PONV, or in administration of antiemetics in the PACU or on the ward (table 4). There were no differences in VAS patient satisfaction scores between the groups at any measurement times.

There was no difference in times to urinary voiding or home readiness between the groups. Voiding was achieved after a median time of 287 (interquartile range 104) min in the neostigmine group (n=43) and 244 (107) min in the saline group (n=42). Home readiness was achieved after 292 (127) min and 249 (130) min in the neostigmine and saline groups, respectively.

Four patients (8%) in the neostigmine group and five (10%) in the saline group were admitted to hospital because of complications related to anaesthesia (PONV, dizziness, pain).

Table 1 Patient characteristics (mean (95% confidence interval (CI) or number of patients). No significant differences

	Neostigmine (n=50)	Saline (n=48)
Age (yr)	34 (32–36)	32 (30–34)
Weight (kg)	59 (57–61)	60 (58–62)
Height (cm)	166 (165–168)	166 (164–168)
History of PONV in previous anaesthesia	8	8
History of motion sickness	17	13
Menstrual cycle (follicular/ovulation/luteal phase)	27/13/6	30/11/3

Table 2 Details of anaesthesia (median (interquartile range)). No significant differences

	Neostigmine	Saline
Duration of anaesthesia (min)	43 (49)	54 (133)
Delay from end of surgery to end of anaesthesia (min)	2 (1)	2 (2)
Extubation time (min)	3 (3)	4 (4)
Mivacurium dose (mg)	18.0 (13.2)	20.6 (12.8)
Alfentanil dose (mg)	0.0 (0.5)	0.0 (0.5)

Table 3 Incidence of postoperative nausea and vomiting (PONV) (numbers of patients with PONV/group size). [a]Home information for five patients was missing; [b]home information for one patient was not available

	Neostigmine	Saline
Post anaesthesia care unit	7/50	8/48
Ward	19/50	24/48
Total PONV at hospital	23/50	25/48
On the way home	8/35	10/38
At home	6/35	9/38
Total PONV for 24 h	25/45[a]	27/47[b]

Table 4 Antiemetic and analgesic medication in the PACU and on the ward. Values are expressed as percentage of patients or median (interquartile range). No significant differences

	Neostigmine	Saline
PACU		
Antiemetics (%)	10	13
Fentanyl (%)	74	85
Fentanyl dose (mg)	0.1 (0.15)	0.1 (0.1)
Ward		
Antiemetics (%)	22	25
Opioids (%)	24	19

Table 5 Worst pain experienced by patients evaluated on a scale 0–3. Values are numbers of patients. *$P<0.05$ between groups

	Neostigmine	Saline
PACU		
No pain/mild/moderate/severe	4/29/15/2	5/28/14/1
Ward		
No pain/mild/moderate/severe	7/33/9/1	9/29/10/0
At home		
No pain/mild/moderate/severe*	8/24/3/0	2/24/10/2

There were no significant differences in fentanyl administration in the PACU or on the ward (table 4.) Distribution of worst pain experienced in the PACU, on the ward and at home is shown in table 5. Patients who received neostigmine experienced less pain at home.

Discussion

Neostigmine and glycopyrrolate for antagonism of neuromuscular block did not increase the incidence of PONV either during the first 90 min after anaesthesia or afterwards.

Nausea or vomiting were uncommon in the PACU (seven patients in the neostigmine group and eight in the saline group). Three of the seven patients in the neostigmine group and seven of the eight patients in the saline group still had symptoms on the ward. In this study, fewer patients had PONV than in a previous sevoflurane study by Eriksson, Haasio and Korttila,[11] where patients undergoing gynaecological laparoscopy were evaluated. We did not encourage patients to drink until on the ward and this may explain the difference. Not drinking before discharge after day-case surgery may reduce PONV.[15] On the ward, where patients drank, ate and ambulated, the incidence of PONV was 38% in the neostigmine group and 50% in the saline group.

Our dose of neostigmine (2 mg) was based on the low intensity of neuromuscular block at the time of antagonism (four of four TOF twitches visible with fade), for which 25 $\mu g\ kg^{-1}$ is the recommended dose.[16] The dose of neostigmine (33 $\mu g\ kg^{-1}$) was also clinically relevant; neostigmine 20 and 40 $\mu g\ kg^{-1}$ after mivacurium infusion combined with propofol anaesthesia has been shown to accelerate recovery of neuromuscular block.

Unplanned hospital admission rate in this study was high (17 of 98 patients) but only nine were admitted to hospital for anaesthetic indications. The explanation may relate to our public health care system. The first overnight stay in hospital does not incur any extra cost for the patient and approximately 30% had a drain in the peritoneal cavity. There were no differences between groups in times to home readiness.

The effect of reversal drugs for neuromuscular block on the occurrence of PONV is not clear, although several studies have been published. In common with previous investigators, we used an anticholinergic drug (glycopyrrolate) with neostigmine to prevent bradycardia. King and colleagues[6] studied elderly patients undergoing orthopaedic surgery. They found that reversal drugs increased the incidence of PONV, but they did not follow the symptoms of their patients. Instead, they interviewed patients and nurses 24 h after surgery. Also, Ding, Fredman and White suggested an increase in PONV in an outpatient population after administration of neostigmine and glycopyrrolate.[9] Their anaesthetic method did not include propofol, and morphine was used to relieve pain. Furthermore, it has been suggested that their observations did not allow definite conclusions to be drawn.[17] Therefore, any comparisons between our results and those of Ding, Fredman and White are difficult. Watcha and colleagues[10] studied the incidence of vomiting in 8–9-yr-old children after halothane anaesthesia. They found that the neostigmine–glycopyrrolate combination was associated with more vomiting in the PACU compared with controls. Unfortunately, nausea was not evaluated. Thus their study design differs from ours. The results of Boeke and colleagues,[8] and our previous report[7] are in agreement with our study. Boeke and colleagues used a smaller dose of neostigmine (1.5 mg) and atropine for antagonism of neuromuscular block in the outpatient setting. In our previous study[7] with women undergoing abdominal hysterectomy, there was no difference between those who received 2 mg of neostigmine with glycopyrrolate and those who received an equal volume of saline.

The mechanisms of PONV are multifactorial, and in the investigation of PONV background factors and factors related to the operation, anaesthesia must be well controlled.[18] Also, assessment of nausea and vomiting should be defined. We used an exact protocol to define the symptoms. Administration of effective antiemetics was predetermined before the study. Furthermore, patients were monitored with frequent interviews.

In our study, patients who had received neostigmine had less pain at home than patients who had received saline. Recently, there has been an increased interest in the role of acetylcholine receptors in pain.[19 20] Furthermore, additional studies are warranted to evaluate whether neostigmine decreases postoperative pain.

We determined the size of the study groups based on our earlier sevoflurane study which demonstrated a high incidence of PONV after sevoflurane.[11] Thus according to power analysis, less than 50 patients were needed in each group to resolve a clinically relevant difference. However, the incidence of PONV was much higher in the previous study than in the present one. At this point, repeated power analysis using the present data showed that several hundred patients in each group would be needed to confirm an 80% chance of finding a 20% difference between groups. Therefore, we conclude that no major effect of reversal drugs on PONV was demonstrated in this study. A larger sample size would be needed to study small differences.

In summary, when using propofol and sevoflurane, we found a low incidence of postoperative nausea or vomiting in this high-risk population, consisting of women undergoing gynaecological laparoscopy. The use of neostigmine with glycopyrrolate did not increase the incidence of PONV.

References

1. Koivuranta M, Laara E, Snare L, Alahuhta S. A survey of postoperative nausea and vomiting. *Anaesthesia* 1997, **52**: 443–449.
2. Kallar SK. Assessing recovery and outcome. In: White PF, ed *Ambulatory Anesthesia and Analgesia*. London: WB Saunders, 1997; 457–464
3. Raeder J, Gupta A, Pedersen FM Recovery characteristics of sevoflurane- or propofol-based anaesthesia for day-care surgery. *Acta Anaesthesiologica Scandinavica* 1997, **41**: 988–994.
4. Bevan DR. Fifty years of muscle relaxants. *Acta Anaesthesiologica Scandinavica* (Suppl.) 1995; **106**: 2–6
5. Lessard MR, Trepanier CA, Rouillard JF Neostigmine requirements for reversal of neuromuscular blockade following an infusion of mivacurium. *Canadian Journal of Anaesthesia* 1997; **44**: 836–842.
6. King MJ, Milazkiewicz R, Carli F, Deacock AR. Influence of neostigmine on postoperative vomiting *British Journal of Anaesthesia* 1988, **61**: 403–406.
7. Hovorka J, Korttila K, Nelskyla K, Soikkeli A, Sarvela J,

Paatero H, Halonen P, Yli-Hankala A. Reversal of neuromuscular blockade with neostigmine has no effect on the incidence or severity of postoperative nausea and vomiting. *Anesthesia and Analgesia* 1997; **85**: 1359–1361

8. Boeke A, de Lange J, van Druenen B, Langemeijer J. Effect of antagonizing residual neuromuscular block by neostigmine and atropine on postoperative vomiting. *British Journal of Anaesthesia* 1994; **72**: 654–656.
9. Ding Y, Fredman B, White PF. Use of mivacurium during laparoscopic surgery: effect of reversal drugs on postoperative recovery. *Anesthesia and Analgesia* 1994; **78**: 450–454.
10. Watcha MF, Safavi FZ, McCulloch DA, Tan TS, White PF. Effect of antagonism of mivacurium-induced neuromuscular block on postoperative emesis in children. *Anesthesia and Analgesia* 1995; **80**: 713–717.
11. Eriksson H, Haasio J, Korttila K. Recovery from sevoflurane and isoflurane anaesthesia after outpatient gynaecological laparoscopy. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 377–380.
12. Eriksson H, Korttila K. Recovery profile after desflurane with or without ondansetron compared with propofol in patients undergoing outpatient gynecological laparoscopy. *Anesthesia and Analgesia* 1996; **82**: 533–538.
13. Nelskyla K, Eriksson H, Soikkeli A, Korttila K. Recovery and outcome after propofol and isoflurane anaesthesia in patients undergoing laparoscopic hysterectomy. *Acta Anaesthesiologica Scandinavica* 1997; **41**: 360–363.
14. Korttila K. Recovery from outpatient anaesthesia. Factors affecting outcome. *Anaesthesia* (Suppl.) 1995; **50**: 22–28.
15. Watcha MF, White PF. Post-operative nausea and vomiting. do they matter? *European Journal of Anaesthesiology* 1995; **10**: 18–23.
16. Lebowitz PW, Ramsey FM. Muscle relaxants. In: Barash PG, Cullen BF, Stoelting RK, eds. *Clinical Anaesthesia.* Philadelphia: JB Lippincott, 1989; 339–370.
17. Boeke A ,White F. Does neostigmine cause nausea and vomiting? *Anesthesia and Analgesia* 1995; **80**: 849.
18. Korttila K. The study of postoperative nausea and vomiting *British Journal of Anaesthesia* 1992; **69**: 20S–23S.
19. Strauss E. New nonopioid painkiller shows promise in animal tests. *Science* 1998; **279**: 32–33.
20. Bannon AW, Decker MW, Holladay MW, Curzon P, Donnelly-Roberts D, Puttfarcken PS, Bitner RS, Diaz A, Dickenson AH, Porsolt RD, Williams M, Arneric SP. Broad-spectrum, non-opioid analgesic activity by selective modulation of neuronal nicotinic acetylcholine receptors. *Science* 1998; **279**: 77–80.

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LABORATORY INVESTIGATIONS

Effects of inhaled oxygen concentration on fat metabolism during propofol infusion in rabbits

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Summary

We have investigated the effect of inhaled oxygen tension on lipid metabolism during propofol infusion. Propofol is supplied as a lipid emulsion containing 10% soybean oil, which is rich in triglycerides (TG). Infused TG are metabolized via three pathways in the liver cell; Krebs cycle, ketogenesis and release as very low density lipoproteins (VLDL) into the blood. For this reason, we measured TG and the products of the three pathways; carbon dioxide, ketone bodies and VLDL. Thirty-two rabbits were anaesthetized under four different conditions: propofol under hyperoxia, normoxia, hypoxia and isoflurane anaesthesia under hyperoxia. Our results indicated that hyperoxia produced more ketone bodies, normoxia more Pa_{CO_2} and hypoxia more free fatty acids (FFA) and TG compared with the other propofol infusion groups. We conclude that hyperoxia during propofol infusion facilitated fat metabolism through ketogenesis, while normoxia did so via the Krebs cycle. Also, hypoxia suppressed utilization of TG and VLDL production in the liver. (*Br. J. Anaesth.* 1998; **81**: 761–765).

Keywords: anaesthetics i.v., propofol; oxygen, tension; metabolism, lipid; rabbit

Diprivan is an i.v. anaesthetic and is used widely for sedation in intensive care units. It is supplied in the form of lipid microspheres containing 10% triglycerides (TG) and 1% propofol. TG are usually metabolized via three pathways in the liver cell; Krebs cycle, ketogenesis and reconstruction as very low density lipoproteins (VLDL).[1] As fat metabolism needs a certain amount of oxygen, it is likely that arterial oxygen tension (Pa_{O_2}) could affect fat metabolism.

In intensive care units, some patients suffering from respiratory dysfunction occasionally show low Pa_{O_2}. In contrast, some patients show high Pa_{O_2} values during artificial ventilation. Accordingly, Pa_{O_2} varies from patient to patient and fat is metabolized via different pathways. Previous studies measured TG, cholesterol and free fatty acids (FFA) during propofol infusion,[2 3] but there are no reports on the relationship between Pa_{O_2} and fat metabolism. Thus we have investigated how inhaled oxygen concentration affects fat metabolic pathways and products during propofol infusion.

Materials and methods

The study was approved by the Research Ethics Committee of Kanazawa University. We studied 32 Japanese white rabbits (Sankyo Laboratory, Toyama, Japan) weighing 3.0–3.5 kg. All animals were given food and water freely before the experiments to avoid starvation and hypoglycaemia which activates fat metabolism. All experiments were started between 09:00 and 10:00. Anaesthesia was induced and maintained with 1–3% isoflurane and oxygen during surgery. A 24-gauge indwelling catheter (Jelco, Critikon, Rome, Italy) was inserted into the otic marginal vein for infusion of propofol, and another into the femoral artery for arterial pressure measurement and blood sampling. Arterial pressure and heart rate were recorded using a conventional monitoring system (2G82, Nihondenki-Sanei, Tokyo, Japan). Lactated Ringer's solution was infused at 10 ml kg^{-1} h^{-1}. After tracheostomy, pancuronium 2 mg was injected and artificial ventilation started using a ventilator (SN-480–5, Shinano, Tokyo, Japan). Tidal volume was set at 15 ml kg^{-1} and positive end-expiratory pressure at 2 cm H_2O. Ventilatory frequency was adjusted to maintain arterial carbon dioxide pressure (Pa_{CO_2}) at 4.0–5.2 kPa, and this rate was maintained throughout the experiment.

After baseline blood samples were obtained from the femoral artery, rabbits were allocated randomly to one of four groups: isoflurane group (inhalation of isoflurane with 100% oxygen), hyperoxia group (propofol infusion with 100% oxygen), normoxia group (propofol infusion with 21% oxygen) and hypoxia group (propofol infusion with 10% oxygen). Administration of isoflurane was continued at 1% for the isoflurane group; for the other groups, isoflurane was terminated and propofol infusion started at a rate of 30 mg kg^{-1} h^{-1}, followed by adjustment of the inhaled oxygen concentration according to group. At 150 min from the start of the assignment, blood samples were obtained. After the experiments were finished, the animals were exsanguinated by propofol and potassium chloride injection.

MEASUREMENTS

To identify the lipid metabolic pathway, the following data were collected; total fat (TF), TG, FFA, VLDL in serum, Pa_{CO_2}, beta-hydroxybutyrate and acetoacetate in plasma, and blood sugar in whole blood. For each samples, 6.5 ml of blood were obtained from the femoral artery catheter at each sampling time.

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Next, 3 ml of the blood sample were centrifuged at 1500 rpm for 10 min in a serum separation tube, and the separated serum was stored at –70°C until analysis.

TF concentration in serum was measured by the sulpho-phospho-vanillin method. TG concentration in serum was measured by Esper A series-TG kit (Nipro, Osaka, Japan), which is a two-step enzymatic method. FFA concentration in serum was measured by NEFA-zyme Eiken kit (Eiken, Tokyo, Japan), which is an acyl-CoA synthetase–acyl-CoA oxidase–peroxidase method. VLDL concentration in serum was measured by BLF-Eiken II kit (Eiken, Tokyo, Japan), which is a precipitation analysis using dextran and calcium sulphate. These serum metabolites were measured at the Sumitomo Bioscience Laboratory (Tokyo, Japan).

Another 2 ml of the blood sample were heparinized and centrifuged at 1500 rpm for 10 min, and the plasma obtained stored under the same conditions as serum. Acetoacetate (ACAC) and beta-hydroxybutyrate (HOB) in plasma were measured using a Keto 340 spectrophotometer (Ihara, Kasugai, Japan) and a Ketorex kit (Sanwa, Nagoya, Japan). The total amount of ketone bodies (TKB) was calculated as the sum of ACAC and HOB. The arterial ketone body ratio (AKBR) was calculated by dividing ACAC by HOB value.

For measurement of propofol concentration, 1 ml of blood sample was used. Samples were heparinized and stored at 4°C until analysis. Propofol concentrations in the samples were assayed within 3 days of sampling using high performance liquid chromatography (LC-10AD, Shimadzu, Kyoto, Japan) with fluorescent detection (Waters 470, Waters Associates, Milford, USA), as described by Plummer.[4] Standard curves for propofol concentrations in whole blood were linear within the range 0.5–15 μg ml^{-1} (r^2=0.97, P<0.01).

The remaining 0.5 ml of blood was used for measurement of Pa_{O_2}, Pa_{CO_2}, pH and bicarbonate ions (HCO_3^-) with an automatic gas analyser (ABL-3, Radiometer, Copenhagen, Denmark). Blood sugar was measured using Actrend (Yamanouchi, Tokyo, Japan).

STATISTICAL ANALYSIS

Values are presented as median (range). Measured values in groups were compared using the Kruskal–Wallis non-parametric ANOVA test. For comparisons within groups, the Wilcoxon signed rank sum test was used. Results were considered statistically significant when P<0.05.

Results

Weight, heart rate and systolic arterial pressure in all four groups were comparable at baseline. At 150 min from the start of the experiments, heart rate in the propofol groups decreased significantly below baseline, while systolic arterial pressure decreased significantly below baseline in all but the normoxia group. At that time, the hypoxia group showed a significantly higher propofol concentration than the other propofol infusion groups (table 1).

Table 1 Physiological data and propofol concentrations. Baseline=data before assignment; 150 min=data at 150 min from assignment. Hyper=hyperoxia group, Normo=normoxia group, Hypo=hypoxia group, Iso=isoflurane group. Values are median (range). Statistical differences (P<0.05) between groups compared with: *Hyper, #Normo, †Hypo and §Iso. ‡Statistical differences within groups

	Hyper (n=8)	Normo (n=8)	Hypo (n=8)	Iso (n=8)
Weight (kg)	3.3 (3.1–3.5)	3.2 (3.0–3.4)	3.3 (3.1–3.5)	3.1 (3.0–3.4)
Heart rate (beat min^{-1})				
Baseline	288 (252–308)	290 (280–304)	284 (258–328)	284 (256–300)
150 min	239 (184–300)‡	258 (216–288)‡	213 (168–248)§‡	268 (256–284)†
Systolic arterial pressure (mm Hg)				
Baseline	122 (107–136)	117 (99–135)	108 (92–126)	117 (87–142)
150 min	111 (96–126)†‡	122 (100–123)†	88 (76–105)*#‡	102 (76–135)‡
Propofol concentration (μg ml^{-1})				
150 min	7.5 (5.7–11.4)	7.6 (5.0–10.2)	14.4 (10.6–16.5)*#	—

Table 2 Blood-gas analysis. Hyper=hyperoxia group, Normo=normoxia group, Hypo=hypoxia group, Iso=isoflurane group. Pa_{O_2}=arterial pressure of oxygen; Pa_{CO_2}=arterial pressure of carbon dioxide, HCO_3^-=bicarbonate ion. Values are median (range). Statistical differences (P<0.05) between groups compared with: *Hyper, #Normo, †Hypo and §Iso. ‡Statistical differences within groups

	Hyper (n=8)	Normo (n=8)	Hypo (n=8)	Iso (n=8)
Pa_{O_2} (kPa)				
Baseline	69.1 (65.1–87.1)	70.3 (55.3–78.5)	74.3 (62.9–76.0)	74.4 (54.3–76.1)
150 min	80.5 (67.2–89.6)#†‡	14.3 (9.6–18.3)*†§‡	6.0 (4.8–6.7)*#§‡	69.7 (65.3–80.0)#†
Pa_{CO_2} (kPa)				
Baseline	4.0 (3.4–5.1)	4.1 (3.6–4.5)	4.5 (3.9–5.8)	4.1 (3.6–4.7)
150 min	4.1 (3.3–4.8)#	5.2 (3.9–5.5)*†§‡	4.2 (3.2–5.0)#	4.2 (3.6–4.7)#
pH				
Baseline	7.444 (7.343–7.551)	7.470 (7.375–7.512)	7.397 (7.370–7.518)	7.378 (7.343–7.516)
150 min	7.414 (7.337–7.487)†	7.375 (7.263–7.473)†‡	7.190 (7.136–7.376)*#§‡	7.424 (7.324–7.511)†
HCO_3^- (mmol)				
Baseline	20.3 (15.3–23.3)	21.6 (20.1–23.6)	22.8 (18.1–24.8)	20.5 (16.3–24.7)
150 min	19.2 (14.7–21.8)†	20.8 (16.7–22.8)†	11.9 (6.1–15.5)*#§‡	19.5 (16.8–22.3)†

Table 3 Serum lipids and blood sugar. TG=triglycerides in serum; FFA=free fatty acid in serum; TF=total fat in serum; VLDL=very low density lipoprotein; BS=blood sugar. Hyper=hyperoxia group, Normo=normoxia group, Hypo=hypoxia group, Iso=isoflurane group. Values are median (range). Statistical differences ($P<0.05$) between groups compared with: *Hyper, #Normo, †Hypo and §Iso. ‡Statistical differences within groups

	Hyper (*n*=8)	Normo (*n*=8)	Hypo (*n*=8)	Iso (*n*=8)
TG (mg dl^{-1})				
Baseline	33 (17–45)	33 (25–55)	34 (28–31)	35 (25–47)
150 min	409 (237–556)†§‡	471 (297–544)†§‡	735 (628–869)*#§‡	48 (42–74)*#†
FFA (mEq litre^{-1})				
Baseline	1.43 (0.95–2.02)	1.55 (1.16–2.24)	1.57 (0.87–2.22)	1.55 (1.22–2.03)
150 min	4.44 (3.64–5.27)†§‡	4.84 (2.39–5.87)†§‡	7.67 (6.48–10.24)*#§‡	1.88 (1.34–2.54)*#†
TF (mg dl^{-1})				
Baseline	171 (135–207)	166 (122–228)	160 (125–222)	167 (126–211)
150 min	702(457–894)†§‡	656 (558–812)†§‡	1215 (989–1654)*#§‡	225 (156–324)*#†
VLDL (mg dl^{-1})				
Baseline	50 (28–102)	45 (21–111)	75 (21–154)	64 (28–105)
150 min	195 (106–314)§‡	195 (124–287)§‡	292 (154–356)§‡	67 (54–115)*#†
BS (mg dl^{-1})				
Baseline	209 (108–340)	161 (98–273)	185 (123–380)	170 (144–345)
150 min	169 (142–290)†	229 (159–328)†	333 (210–358)*#§‡	189 (167–256)†

Table 4 Ketone body concentrations. ACAC=acetoacetate concentration in plasma; HOB=beta-hydroxy butyrate concentration in plasma; TKB=total ketone bodies concentration; AKBR=arterial ketone body ratio. Hyper=hyperoxia group, Normo=normoxia group, Hypo=hypoxia group, Iso=isoflurane group. Values are median (range). Statistical differences ($P<0.05$) between groups compared: *with Hyper, #Normo, †Hypo and §Iso. ‡Statistical differences within groups

	Hyper (*n*=8)	Normo (*n*=8)	Hypo (*n*=8)	Iso (*n*=8)
ACAC (µmol litre^{-1})				
Baseline	51 (26–102)	44 (15–89)	44 (16–68)	46 (18–59)
150 min	179 (131–254)#†§‡	78 (59–90)*†‡	14 (6–39)*#§‡	32 (26–77)*
HOB (µmol litre^{-1})				
Baseline	61 (40–119)	70 (46–112)	47 (34–83)	57 (35–69)
150 min	311 (284–661)#†§‡	125 (71–178)*‡	103 (61–174)*‡	53 (47–88)*
TKB (µmol litre^{-1})				
Baseline	112 (66–220)	123 (61–201)	86 (55–138)	96 (59–121)
150 min	490 (422–896)#†§‡	201 (130–267)*‡	130 (67–198)*	85 (77–165)*
AKBR				
Baseline	0.75 (0.45–1.17)	0.55 (0 33–1.07)	0.74 (0.32–1.21)	0.68 (0.45–0 93)
150 min	0.57 (0.36–0.65)†‡	0.66 (0.43–0.88)†	0.14 (0.09–0.39)*#§‡	0.58 (0.42–0.88)†

Blood-gas analysis at baseline was comparable between groups. At 150 min, Pa_{O_2} was significantly different between the propofol infusion groups. Pa_{CO_2} in the normoxia group increased significantly compared with baseline, but was unchanged in the other three groups. pH in the normoxia group decreased significantly below baseline values. pH and HCO_3^- in the hypoxia group were significantly lower than baseline values or values in the other groups (table 2).

TF, TG, FFA and VLDL in the four groups were not significantly different at baseline. At 150 min, all of these variables in the propofol infusion groups increased significantly compared with baseline values. Moreover, all blood samples obtained from the propofol infusion groups showed lipaemia. For the hypoxia group, values of TG, FFA and TF were significantly higher than those in the other groups, but VLDL was not significantly different compared with the other propofol infusion groups. Blood sugar values were comparable, with only the hypoxia group showing a significantly higher blood sugar concentration than the other groups at 150 min (table 3).

ACAC and HOB at baseline were also comparable. At 150 min, all propofol infusion groups had significant increases in ACAC, HOB and TKB, except for ACAC in the hypoxia group. The hyperoxia group showed significantly higher and the hypoxia group significantly lower ACAC concentrations than the other propofol infusion groups. HOB and TKB were significantly higher in the hyperoxia group. Finally, AKBR was significantly lower in the hypoxia group (table 4).

Discussion

Diprivan is supplied as lipid microspheres made from soybean oil containing 10% TG. The microspheres are metabolized, as shown in figure 1.[5] The infused microspheres consist of TG sequentially subtracted by lipoprotein lipase. TG trapped by the liver cell is dissociated into FFA and glycerol. The latter is then metabolized via the Krebs cycle, which produces ATP but requires much oxygen and part of the FFA is metabolized into acetyl-coenzyme A (acetyl-CoA) in the mitochondrion (beta-oxidation). Allocation of acetyl-CoA to either ketogenesis or the Krebs cycle is controlled by liver mitochondrial ATP concentrations. When ATP is high, acetyl-CoA enters the ketogenesis pathway, as ketogenesis produces less ATP than the Krebs cycle.[1] Remaining FFA is resynthesized as VLDL and released into the blood. Thus oxygen supply which regulates ATP concentrations in the liver cell is an important factor for determining the pathway of TG metabolism.

While Pa_{CO_2}, ketone bodies, TG, FFA, TF and

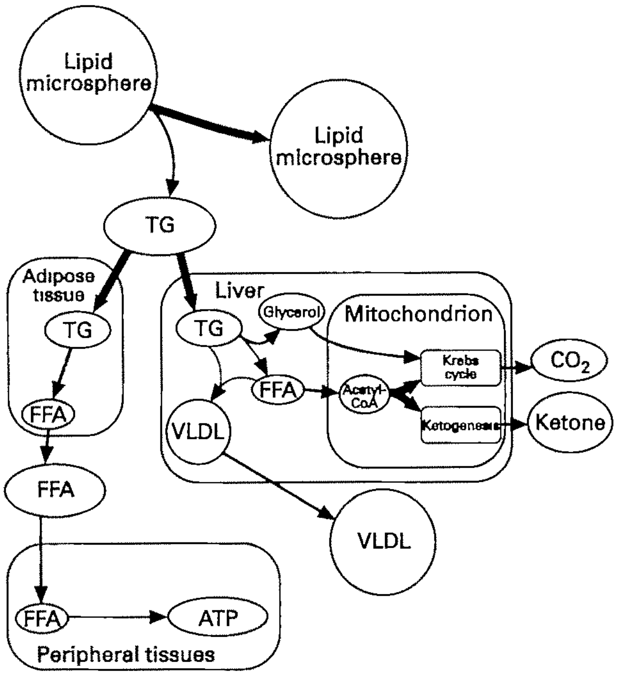

Figure 1 Schematic diagram of metabolic pathways for fat. Triglycerides (TG) are metabolized via three pathways in the liver: Krebs cycle, ketogenesis and release as very low density lipoproteins (VLDL) into blood. TG are stored or metabolized into free fatty acid (FFA) in adipose tissue. TG and FFA are used as energy sources in peripheral tissues such as muscle or heart.

VLDL did not increase compared with baseline in the isoflurane group, most of these variables increased significantly in the propofol infusion groups, indicating that these increases were caused by infusion of propofol. In the hyperoxia group which was supplied with excess oxygen, ketone body concentrations in arterial blood were significantly higher than in the other propofol infusion groups. This could be explained by the fact that hyperoxia increases ATP in the liver mitochondrion, causing acetyl-CoA to be metabolized through the ketogenic pathway. As humans have a large capacity for consuming ketone bodies, ketosis (1000–3000 µmol litre^{-1}) or ketoacidosis (>3000 µmol litre^{-1}) seldom occurs. Canivet and colleagues[6] reported massive ketonuria during propofol infusion but this disappeared soon after termination of infusion. In our study, ketosis or ketoacidosis were not observed, probably because of the short infusion time.

In the normoxia group, Pa_{CO_2} was significantly higher than in the other groups. Under normoxia, the liver mitochondria oxidizes acetyl-CoA via the Krebs cycle to produce ATP efficiently. Moreover, glycerol, which is another byproduct of TG, is also metabolized via the Krebs cycle, so that more ATP and carbon dioxide are produced under normoxia. This phenomenon is known as stimulation of respiration by FFA.[7] The increase in carbon dioxide may become an additional burden when propofol is given to patients with respiratory dysfunction.

While FFA, TG and TF in the hypoxia group increased significantly compared with the other groups, VLDL did not show any significant change. This is accounted for by the finding that infused emulsion produces TG via lipoprotein lipase in the blood and TG is metabolized into FFA in adipose tissues.[1] Peripheral tissues generally use TG and FFA to produce ATP, but hypoxia suppresses this because of insufficient oxygen and ATP. Hence, FFA, TG and TF in serum increase. In addition, VLDL is synthesized from TG and FFA in the liver. This process also needs ATP, which is why VLDL did not increase in the hypoxia group.

In our study, the hypoxia groups showed no change in TKB and a reduction in AKBR. Hence acetyl-CoA is metabolized not by ketogenesis but via the Krebs cycle under hypoxia to generate more ATP. Ketone bodies and nicotine amide (NAD) are in equilibrium when:

$$\mathrm{ACAC+NADH \leftrightarrows HOB+NAD^+}$$

Hypoxia shifts this equilibrium to the right, thus producing free NAD$^+$ which can generate ATP. Accordingly, the ratio of ACAC to HOB (=AKBR) decreases under hypoxia.[8]

In the hypoxia group, heart rate and systolic arterial pressure decreased. These reductions can be explained by the existence of high blood propofol concentrations, hypoxia and high concentrations of FFA. Hypoxia increases propofol concentrations because of depression of metabolic rate[9] and suppression of the circulatory system.[10] Hypoxia and metabolic acidosis also suppress cardiac function.[11] FFA and hypoxia synergistically attenuate myocardial contractility.[12] Thus infusion of propofol under hypoxia may depress haemodynamic function. Moreover, reduced hepatic perfusion caused by this haemodynamic depression would decrease propofol and lipid clearance by the liver.

Care should be taken in the application of our results to humans, because rabbits are herbivores and have a small capacity for metabolizing lipids. Moreover, they were given an infusion of a larger dose of propofol (30 mg kg^{-1} h^{-1}) than is usual for humans (4–10 mg kg^{-1} h^{-1}). In fact, adult humans seldom manifest hypertriglycaemia during infusion of propofol. Paediatric patients, especially neonates, have a smaller capacity for metabolizing lipids than adults, and this may cause the fat-overload syndrome.[13] This syndrome constitutes an unusual but fatal complication of i.v. lipid administration. Parke and colleagues[14] reported the death of five children who underwent mechanical ventilation with propofol sedation. Their symptoms were characterized by lipaemia, hepatosplenomegaly, bradycardia, metabolic acidosis and fever, all of which are similar to the symptoms of the fat-overload syndrome. In contrast, Pepperman and Macrae[15] reported that infusion of propofol for sedation in paediatric patient still compares favourably with other sedative agents although it sometimes causes metabolic acidosis or lipaemia.

In summary, we found that hyperoxia caused ketosis, but reduction of propofol infusion rate or inhaled oxygen tension reduced the level of ketone bodies. In the case of long-term propofol infusion, urine should be tested regularly for ketonuria. Hypoxia caused accumulation of FFA and TG, increase in propofol concentrations and suppression of haemodynamic function. Thus propofol should be used cautiously in patients who might become hypoxic. Maintaining normoxia is therefore recommended during long-term infusion of propofol. In addition, Pa_{CO_2} should be measured regularly.

References

1. Mayes PA. Oxidation of fatty acid: Ketogenesis. In: Murray RK, Granner DK, Mayes PA, Rodwell VW, eds. *Harper's Biochemistry*, 23rd Edn. East Norwalk: Appleton and Lange, 1993; 220–231.
2. Eddleston JM, Shelly MP. The effect on serum lipid concentrations of a prolonged infusion of propofol—hypertriglyceridaemia associated with propofol administration. *Intensive Care Medicine* 1991; **17**: 424–426.
3. Gottardis M, Khunl-Brady KS, Koller W, Sigl G, Hackl JM. Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. *British Journal of Anaesthesia* 1989; **62**: 393–396.
4. Plummer GF. Improved method for the determination of propofol in blood by high-performance liquid chromatography with fluorescence detection. *Journal of Chromatography* 1987; **421**: 171–176.
5. Umezawa K, Karino A, Hayashi M, Tahara K, Kimura A, Awazu S. Hepatic uptake of lipid-soluble drugs from fat emulsion. *Journal of Pharmacobiodynamics* 1991; **14**: 591–598.
6. Canivet JL, Gustad K, Leclercq P, Damas P, Lamy M. Massive ketonuria during sedation with propofol in a 12 year old girl with severe head trauma. *Acta Anaesthesiologica Belgica* 1994; **45**: 19–22.
7. Nobes CD, Hay WW, Brand MD. The mechanism of stimulation of respiration by fatty acid in isolated hepatocytes. *Journal of Biological Chemistry* 1990; **265**: 12910–12915.
8. Ozawa K, Aoyama H, Yasuda K, Shimahara Y, Nakatani T, Tanaka J, Yamamoto M, Kamiyama Y, Tobe T. Metabolic abnormalities associated with postoperative organ failure. A redox theory. *Archives of Surgery* 1983; **118**: 1245–1251.
9. Audibert G, Saunier CG, du-Souich P. In vivo and in vitro effects of cimetidine, inflammation, and hypoxia on propofol kinetics. *Drug Metabolism and Disposition* 1993; **21**: 7–12.
10. Hug C jr, McLeskey CH, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, Walawander CA, White PF, Apfelbaum JL, Grasela TH. Hemodynamic effects of propofol: data from over 25,000 patients. *Anesthesia and Analgesia* 1993; 77: S21–S29.
11. Beierholm EA, Grantham RN, O'Keefe DD, Laver MB, Daggett WM. Effects of acid–base changes, hypoxia, and catecholamines on ventricular performance. *American Journal of Physiology* 1975; **228**: 1555–1561.
12. Henderson AH, Most AS, Parmley WW, Gorlin R, Sonnenblick EH. Depression of myocardial contractility in rats by free fatty acids during hypoxia. *Clinical Research* 1970; **26**: 439–449.
13. Heyman MB, Storch S, Ament ME. The fat overload syndrome. Report of a case and literature review. *American Journal of Diseases of Childhood* 1981; **135**: 628–630.
14. Parke TJ, Stevens JE, Rice AS, Greenaway CL, Bray RJ, Smith PJ, Waldmann CS, Verghese C. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *British Medical Journal* 1992; **305**: 613–616.
15. Pepperman ML, Macrae D. A comparison of propofol and other sedative use in paediatric intensive care in the United Kingdom. *Paediatric Anaesthesia* 1997; **7**: 143–153

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Thiopental and propofol impair relaxation produced by ATP-sensitive potassium channel openers in the rat aorta

H. KINOSHITA, K. ISHIDA AND T. ISHIKAWA

Summary

ATP-sensitive potassium channel openers are used as vasodilators in the treatment of cardiovascular disorders. The effects of i.v. anaesthetics on arterial relaxation induced by ATP-sensitive potassium channel openers have not been studied. Therefore, in this study, we have examined if thiopental (thiopentone) and propofol affect the vascular response to the ATP-sensitive potassium channel openers, cromakalim and pinacidil, in the isolated rat aorta. Rings of rat thoracic aortas without endothelium were suspended for isometric force recording. Concentration–response curves were obtained in a cumulative manner. During submaximal contractions with phenylephrine 0.3 µmol litre^{-1}, relaxation after cromakalim 0.1–30 µmol litre^{-1}, pinacidil 0.1–30 µmol litre^{-1} and papaverine 0.1–300 µmol litre^{-1} was demonstrated. Thiopental 30–300 µmol litre^{-1}, propofol 10–100 µmol litre^{-1}, 10% Intralipid 45 µl or glibenclamide 5 µmol litre^{-1} were applied 15 min before addition of phenylephrine. During contractions with phenylephrine, cromakalim and pinacidil induced concentration-dependent relaxation. A selective ATP-sensitive potassium channel antagonist, glibenclamide 5 µmol litre^{-1}, abolished this relaxation, whereas it did not affect relaxation produced by papaverine. Thiopental concentrations >30 µmol litre^{-1} significantly impaired relaxation produced by cromakalim or pinacidil. Propofol concentrations >10 µmol litre^{-1} also significantly reduced relaxation produced by cromakalim or pinacidil, whereas Intralipid was ineffective. Thiopental 300 µmol litre^{-1} and propofol 100 µmol litre^{-1} did not alter relaxation produced by papaverine. These results suggest that the i.v. anaesthetics, thiopental and propofol, impaired vasodilatation mediated by ATP-sensitive potassium channels in vascular smooth muscle cells. (*Br. J. Anaesth.* 1998; **81**: 766–770).

Keywords: anaesthetics i.v., propofol; anaesthetics i.v., thiopental, pharmacology, cromakalim; pharmacology, pinacidil; ions, potassium; ions, ion channels; rat

It has been demonstrated that ATP-sensitive potassium channels play an important role in mediation of vasodilator responses induced by many physiological and pathophysiological stimuli, including acidosis,[1] hypercapnia,[2] hypoxia,[3] nitric oxide,[4] cyclic AMP and cyclic GMP,[5] and receptor agonists.[6–8] ATP-sensitive potassium channel openers are used as therapeutic tools for cardiovascular disorders such as hypertension, angina pectoris and congestive heart failure.[9] Studies on cardiac myocytes have demonstrated that the i.v. anaesthetics, thiopental and propofol, can suppress the delayed rectifier and/or inward rectifier potassium currents.[10–12] However, little is known of the effects of anaesthetics on vasodilatation via potassium channels in vascular smooth muscle cells. Therefore, we have examined the effects of thiopental and propofol on vasodilatation mediated by ATP-sensitive potassium channels by examining if these drugs modify relaxation produced by the ATP-sensitive potassium channel openers, cromakalim and pinacidil, in the isolated rat thoracic aorta.

Materials and methods

The study was approved by the Institutional Animal Care and Use Committee. The experiments were performed on 3-mm thoracic aortic rings obtained from male Wistar–Kyoto rats (300–350 g), anaesthetized with pentobarbital sodium 50 mg kg^{-1} i.p. Rings were studied in modified Krebs–Ringer bicarbonate solution (control solution) of the following composition (mmol litre^{-1}): NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0, calcium EDTA 0.026 and glucose 11.1. In all rings, endothelium was removed mechanically and endothelial removal was confirmed by the absence of relaxation to acetylcholine 10 µmol litre^{-1}. Several rings cut from the same artery were studied in parallel. Each ring was connected to an isometric force transducer and suspended in an organ chamber filled with 25 ml of control solution (37°C, pH 7.4) bubbled with 94% oxygen–6% carbon dioxide. Arteries were gradually stretched to the optimal point of the length–tension curve, as determined by contraction with phenylephrine 0.3 µmol litre^{-1}. In most of the arteries studied, optimal tension was achieved at approximately 1.5 g. Preparations were equilibrated for 90 min. During submaximal contractions to phenylephrine 0.3 µmol litre^{-1}, concentration–response curves to cromakalim 0.1–30 µmol litre^{-1}, pinacidil 0.1–30 µmol litre^{-1} or papaverine 0.1–300 µmol litre^{-1} were obtained in the absence or presence of thiopental, propofol, Intralipid or glibenclamide. Concentration–response curves were obtained in a

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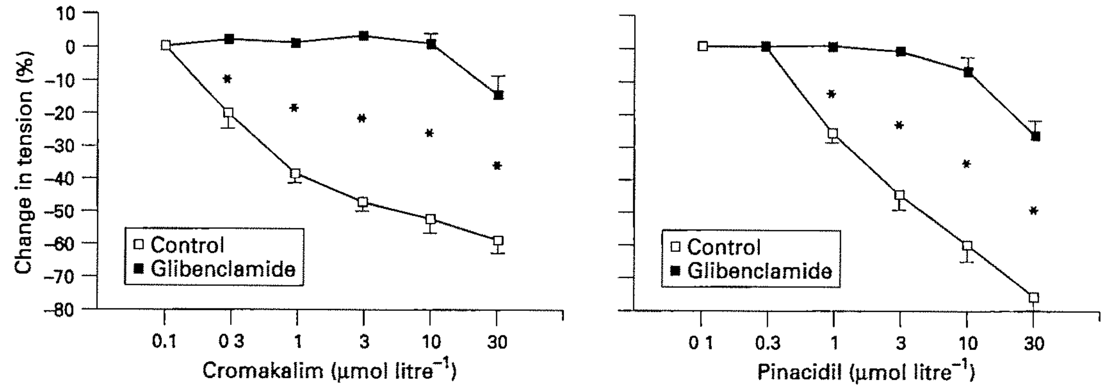

Figure 1 Concentration–response curves for cromakalim 0.1–30 μmol litre^{-1} and pinacidil 0.1–30 μmol litre^{-1} in the absence and presence of glibenclamide 5 μmol litre^{-1}, obtained in rat thoracic aortas without endothelium Data are mean, SEM and expressed as percent of maximal relaxation induced by papaverine 300 μmol litre^{-1}; 100%=860 (10) mg (n=6) and 820 (50) mg (n=6) for control and glibenclamide, respectively (left) and 100%=633 (59) mg (n=6) and 580 (87) mg (n=6) for control and glibenclamide, respectively (right). *P< 0.05 between control rings and rings treated with glibenclamide.

cumulative manner. Only one concentration–response curve was made from each ring. Thiopental, propofol, Intralipid or glibenclamide was given 15 min before addition of phenylephrine 0.3 μmol litre^{-1}. Propofol was applied in its commercially available 10% Intralipid emulsion (10% soybean oil, 2.25% glycerol and 1.2% purified phospholipid).

In a separate series of experiments, the volume of 10% Intralipid 45 μl, identical to that administered to obtain the highest concentration of propofol (100 μmol litre^{-1}), was used. Papaverine 300 μmol litre^{-1} was added at the end of the response to cromakalim or pinacidil to produce maximal relaxation of arteries. Relaxation was expressed as percentage of maximal relaxation to papaverine 300 μmol litre^{-1}.

The following pharmacological agents were used: cromakalim, dimethyl sulphoxide (DMSO), glibenclamide, papaverine hydrochloride, phenylephrine (Sigma, St. Louis, MO, USA), pinacidil (ICN Biomedicals Inc., Aurora, O), propofol (Diprivan; Zeneca Pharmaceutical Co., Osaka, Japan), thiopental sodium (Tanabe Pharmaceutical Co., Osaka, Japan), and 10% Intralipid (Ohtsuka Pharmaceutical Co., Tokyo, Japan). Drugs were dissolved in distilled water such that volumes of <0.15 ml were added to the organ chambers. Stock solutions of cromakalim 30 μmol litre^{-1}, pinacidil 30 μmol litre^{-1} and glibenclamide 5 μmol litre^{-1} were prepared in DMSO 50–160 μmol litre^{-1}.[1] Concentrations of drugs are expressed as final molar (mol litre^{-1}) concentration.

STATISTICAL ANALYSIS

Data are expressed as mean (SEM); n=number of rats from which the aortas were obtained. Statistical analysis was performed using one-way ANOVA, followed by Fisher's test. Differences were considered to be statistically significant when P<0.05.

Results

Initially, we examined the effects of a selective ATP-sensitive potassium channel antagonist, glibenclamide, on relaxation produced by cromakalim and pinacidil to demonstrate if these potassium channel openers selectively produced relaxation mediated by ATP-sensitive potassium channels. In figure 1, concentration–response curves for cromakalim and pinacidil in the absence and presence of glibenclamide are shown. During submaximal contractions with phenylephrine 0.3 μmol litre^{-1}, cromakalim 0.1–30 μmol litre^{-1} and pinacidil 0.1–30 μmol litre^{-1} induced concentration-dependent relaxation. In arteries treated with glibenclamide 5 μmol litre^{-1}, relaxation produced by cromakalim and pinacidil was abolished. The same concentration of glibenclamide did not affect relaxation to the non-selective vasodilator, papaverine 0.1–300 μmol litre^{-1} (table 1).

The effects of thiopental and propofol on relaxation produced by cromakalim, pinacidil and papaverine were then examined to determine if these agents selectively modified relaxation mediated by ATP-sensitive potassium channels. Thiopental significantly impaired relaxation produced by cromakalim and pinacidil in a concentration-dependent manner (fig. 2). Propofol also significantly reduced relaxation produced by cromakalim and pinacidil in a concentration-dependent manner (fig. 3), whereas 10% Intralipid did not affect these responses (data not shown). In contrast, even the highest concentrations of thiopental (300 μmol litre^{-1}) and propofol (100 μmol litre^{-1}) did not alter relaxation produced by papaverine (fig. 4) or affect basal tone (data not shown). Maximal relaxation to papaverine 300 μmol litre^{-1} in arteries treated with these agents was not different compared with that of control arteries (see legends to figs 2–4).

Discussion

In this study, we have demonstrated that: (1) the ATP-sensitive potassium channel openers, cromakalim and pinacidil, produced arterial relaxation which was inhibited by a selective ATP-sensitive potassium channel antagonist, glibenclamide; (2) the

Table 1 Effect of glibenclamide 5 μmol litre^{-1} on relaxations produced by papaverine in rat thoracic aortas without endothelium. Data are mean (SEM)

	$-\log EC_{50}$	Maximal relaxation (mg)
Control	4.9 (0 1)	808 (74)
Glibenclamide	4.9 (0.1)	768 (39)

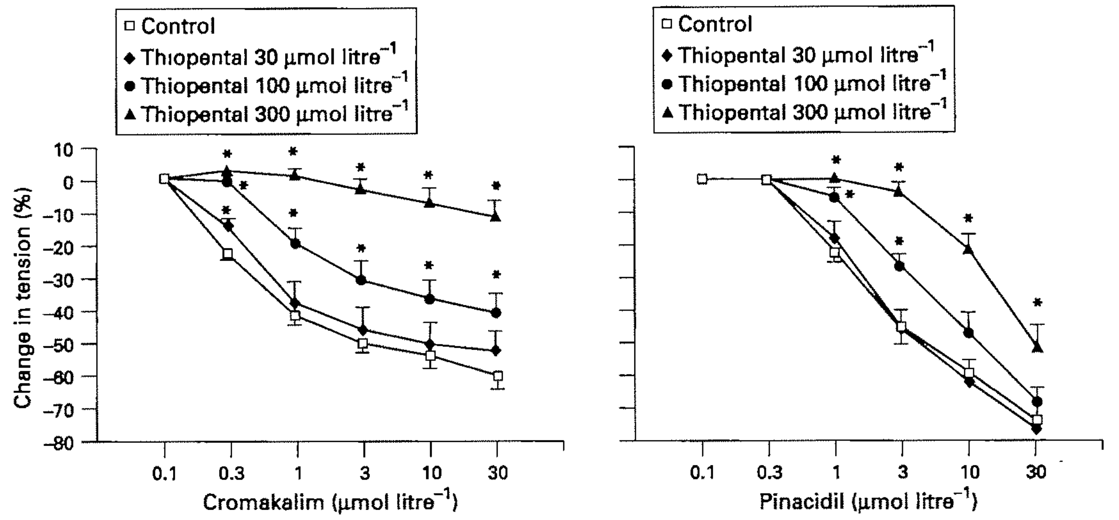

Figure 2 Concentration–response curves for cromakalim and pinacidil in the absence and presence of thiopental 30, 100 and 300 μmol litre^{-1}, obtained in rat thoracic aortas without endothelium. Data are mean, SEM and expressed as percent of maximal relaxation induced by papaverine 300 μmol litre^{-1}; 100%=980 (70) mg (*n*=6), 970 (70) mg (*n*=6), 910 (80) mg (*n*=6) and 900 (120) mg (*n*=6) for control rings and rings treated with thiopental 30, 100 and 300 μmol litre^{-1}, respectively (left) and 100%=695 (43) mg (*n*=5), 674 (55) mg (n=5), 696 (75) mg (*n*=5) and 560 (44) mg (*n*=5) for control rings and rings treated with thiopental 30, 100 and 300 μmol litre^{-1}, respectively (right). *P< 0.05 between control rings and rings treated with thiopental.

i.v. anaesthetics, thiopental and propofol, reduced relaxation produced by cromakalim and pinacidil in a concentration-dependent manner; and (3) these anaesthetics did not alter relaxation produced by papaverine. These results suggest that thiopental and propofol impair vasodilatation mediated by ATP-sensitive potassium channels in smooth muscle cells.

It has been demonstrated that cromakalim and pinacidil are selective ATP-sensitive potassium channel openers[13] and they cause efflux of potassium ions and subsequent hyperpolarization of vascular smooth muscle cells.[6] The sulphonylurea, glibenclamide, has been shown to be a selective antagonist of ATP-sensitive potassium channels acting via the sulphonylurea receptors of these channels but it does not affect the activity of calcium channels, inward rectifier, delayed rectifier or calcium-dependent potassium channels[6 8 13] Therefore, our findings that in endothelium denuded rat thoracic aortas glibenclamide abolished relaxation produced by cromakalim and pinacidil, whereas it did not alter relaxation produced by the non-selective vasodilator, papaverine, suggest that relaxation by cromakalim and pinacidil is mediated by ATP-sensitive potassium channels in smooth muscle cells, reinforcing previous conclusions concerning the selectivity of cromakalim and pinacidil for this class of channel.[6 8 13]

In the rat aorta, thiopental and propofol but not Intralipid, significantly reduced relaxation produced by cromakalim and pinacidil, whereas these anaesthetics did not affect relaxation produced by papaverine, indicating that thiopental and propofol selectively decreased relaxation to ATP-sensitive potassium channel openers. These results suggest

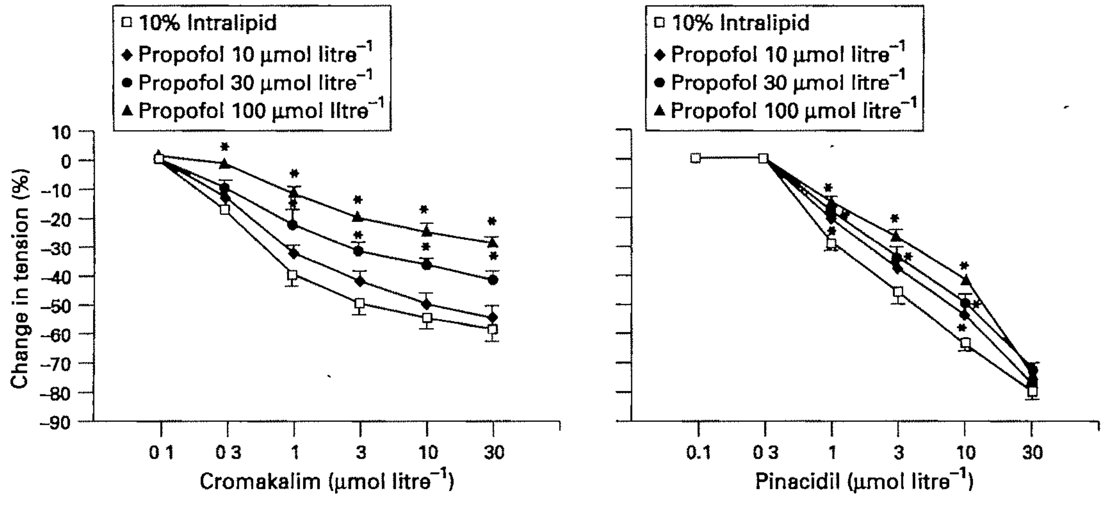

Figure 3 Concentration–response curves for cromakalim and pinacidil in the presence of 10% Intralipid 45 μl and propofol 10, 30 and 100 μmol litre^{-1}, obtained in rat thoracic aortas without endothelium. Data are mean, SEM and expressed as percent of maximal relaxation induced by papaverine 300 μmol litre^{-1}; 100%=970 (60) mg (*n*=6), 950 (30) mg (*n*=6), 920 (80) mg (*n*=6) and 810 (90) mg (*n*=6) for rings treated with 10% Intralipid, and propofol 10, 30 or 100 μmol litre^{-1}, respectively (left), and 100%=880 (114) mg (*n*=4), 860 (95) mg (*n*=4), 840 (69) mg (*n*=4) and 720 (57) mg (*n*=4) for rings treated with 10% Intralipid, and propofol 10, 30 and 100 μmol litre^{-1}, respectively (right). *P< 0.05 between rings treated with 10% Intralipid and those treated with propofol.

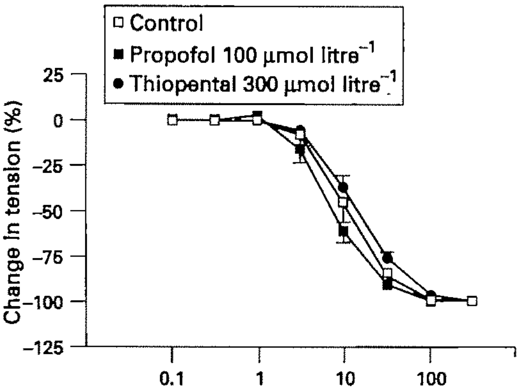

Figure 4 Concentration–response curves for papaverine 0.1–300 µmol litre^{-1} in the absence and presence of propofol 100 µmol litre^{-1} and thiopental 300 µmol litre^{-1}, obtained in rat thoracic aortas without endothelium. Data are mean, SEM and expressed as percent of maximal relaxation induced by papaverine 300 µmol litre^{-1}; 100%=808 (74) mg (n=5), 680 (80) mg (n=5) and 680 (47) mg (n=5) for control rings and rings treated with propofol 100 µmol litre^{-1} and thiopental 300 µmol litre^{-1}, respectively.

that thiopental and propofol reduce vasodilatation mediated by ATP-sensitive potassium channels in vascular smooth muscle cells. Previous studies in cardiac myocytes[10–12] and in isolated blood vessels[14 15] illustrated similar inhibitory effects of these anaesthetics on the activity of potassium channels other than ATP-sensitive ones. In cardiac myocytes, thiopental suppressed delayed rectifier and inward rectifier potassium currents, whereas propofol suppressed only the latter.[10–12] In carotid and renal arteries, thiopental reduced relaxation produced by endothelium-derived hyperpolarizing factor, which causes activation of calcium-dependent potassium channels in smooth muscle cells.[14 15] The precise mechanism of effects of thiopental and propofol on these potassium channels, including ATP-sensitive potassium channels, remains to be determined.

In this study, thiopental and propofol appeared to inhibit relaxation produced by cromakalim more effectively than pinacidil. These results may in part be a result of the differential vasodilator potencies of these ATP-sensitive potassium channel openers. Indeed, in our experimental conditions, cromakalim produced better relaxation at lower concentrations compared with pinacidil, whereas relaxation with these compounds was similar at higher concentrations. These results are consistent with a previous observation that cromakalim is a more potent vasodilator than pinacidil.[13] It is likely that differences in chemical structure between benzopyran and pyridine compounds are responsible for differential vasodilator effects of these ATP-sensitive potassium channel openers.[9]

Thiopental, in the concentrations used in our study, has been shown in myocytes to modestly affect voltage-dependent calcium currents compared with delayed rectifier potassium currents,[11] indicating that thiopental may be less effective on calcium channels. In rat aortas, similar concentrations of thiopental did not alter concentrations of intracellular calcium in arteries treated with potassium chloride, suggesting that it does not affect regulatory mechanisms to increase intracellular calcium in vascular smooth muscle cells.[16 17] Therefore, it is likely that in vascular smooth muscle cells, thiopental preferentially impairs the activity of potassium channels over calcium channels.

A previous study in the rat aorta demonstrated that propofol antagonized voltage-dependent calcium channels in vascular smooth muscle cells.[18] Studies in cardiac myocytes also demonstrated that propofol suppressed L-type voltage-dependent calcium currents.[11 12] In our study, propofol reduced relaxation to ATP-sensitive potassium channels, whereas the dose required was higher than needed to block voltage-dependent calcium channels in vascular smooth muscle cells.[18] Therefore, it appears that in vascular smooth muscle, voltage-dependent calcium channels may be more sensitive to propofol than ATP-sensitive potassium channels.

Plasma concentrations of thiopental and propofol during induction of anaesthesia in humans have been reported as up to 450 µmol litre^{-1} and 30 µmol litre^{-1} for thiopental and propofol, respectively.[19–22] Considering that these drugs bind substantially to plasma proteins, free plasma concentration would be less. Our concentrations of thiopental and propofol that demonstrated inhibition of vasodilatation via ATP-sensitive potassium channels may be higher than expected free plasma concentrations after an induction dose, especially for propofol. However, in the field of neurosurgery and neurological intensive care, high-dose barbiturates are used as a tool for cerebral protection in brain ischaemic patients,[23] and in these cases free plasma concentrations of barbiturate are comparable with the concentrations examined in our study. Although burst suppression doses of propofol are also available for cerebral protection, the effective free plasma concentrations of propofol are lower than the concentrations used in our study.[24] Thus in vascular smooth muscle cells, these i.v. anaesthetics, particularly thiopental, may alter the vasodilator effect of ATP-sensitive potassium channel openers in clinical situations.

It is important to note that the inhibitory effects of thiopental and propofol on relaxation of ATP-sensitive potassium channel openers were demonstrated in arteries without endothelium. ATP-sensitive potassium channel openers can be used as vasodilators for patients with cardiovascular disorders, including hypertension.[9] It has been demonstrated that in these patients, endothelial function is impaired, resulting in decreased endothelium-dependent relaxation.[25] Therefore, our results in the preparations without endothelium indicate that thiopental and propofol may affect the vasodilator effects of ATP-sensitive potassium channel openers, particularly in patients with endothelial dysfunction.

Activation of ATP-sensitive potassium channels plays an important role in circulatory regulation. A recent study demonstrated that cromakalim completely dilated basilar arteries during vasospasm after subarachnoid haemorrhage, suggesting that activation of ATP-sensitive potassium channels may restore cerebral blood flow in brain tissues perfused by vasospastic cerebral arteries.[26] In addition, previous findings demonstrated that acidosis, decreased concentrations of intracellular ATP and increased concentrations of intracellular ADP, concurrently with hypoxia and ischaemia, can activate ATP-sensitive potassium channels, leading to arterial dilatation and/or increased tolerance of tissues to ischaemia.[1 3 7] Therefore, our results suggest that in such physiologically and pathologically induced activation of ATP-sensitive potassium channels, i.v. anaesthetics may impair the beneficial vasodilator responses mediated by ATP-sensitive potassium channels.

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References

1. Kinoshita H, Katusic ZS. Role of potassium channels in relaxations of isolated canine basilar arteries to acidosis. *Stroke* 1997; **28**: 433–438.
2. Faraci FM, Breese KR, Heistad DD. Cerebral vasodilation during hypercapnia: Role of glibenclamide-sensitive potassium channels and nitric oxide. *Stroke* 1994; **25**. 1679–1683.
3. Taguchi H, Heistad DD, Kitazono T, Faraci FM. ATP-sensitive K$^+$ channels mediate dilatation of cerebral arterioles during hypoxia. *Circulation Research* 1994; 74: 1005–1008.
4. Murphy ME, Brayden JE. Nitric oxide hyperpolarizes rabbit mesenteric arteries via ATP-sensitive potassium channels. *Journal of Physiology (London)* 1995; **486**: 47–58.
5. Paterno R, Faraci FM, Heistad DD. Role of Ca^{2+}-dependent K$^+$ channels in cerebral vasodilatation induced by increases in cyclic GMP and cyclic AMP in the rat. *Stroke* 1996; **27**: 1603–1608.
6. Nelson MT, Quayle JM. Physiological roles and properties of potassium channels in arterial smooth muscle. *American Journal of Physiology* 1995; **268**: C799–C822.
7. Heurteaux C, Lauritzen I, Widmann C, Lazdunski M. Essential role of adenosine, adenosine A1 receptors, and ATP-sensitive K$^+$ channels in cerebral ischemic preconditioning. *Proceedings of the National Academy of Sciences USA* 1995; **92**: 4666–4670.
8. Standen NB, Quayle JM, Davies NW, Brayden JE, Huang Y, Nelson MT. Hyperpolarizing vasodilators activate ATP-sensitive K$^+$ channels in arterial smooth muscle. *Science* 1989; **245**: 177–180.
9. Cook NS. The pharmacology of potassium channels and their therapeutic potential. *Trends in Pharmacological Sciences* 1988; **9**: 21–28.
10. Baum VC. Distinctive effects of three intravenous anesthetics on the inward rectifier (I_{K1}) and the delayed rectifier (I_K) potassium currents in myocardium. Implications for the mechanism of action. *Anesthesia and Analgesia* 1993; **76**: 18–23.
11. Sakai F, Hiraoka M, Amaha K. Comparative actions of propofol and thiopentone on cell membranes of isolated guinea pig ventricular myocytes. *British Journal of Anaesthesia* 1996; **77**: 508–516.
12. Buljubasic N, Marijic J, Berczi V, Supan DF, Kampine JP, Bosnjak ZJ. Differential effects of etomidate, propofol, and midazolam on calcium and potassium channel currents in canine myocardial cells. *Anesthesiology* 1996; **85**: 1092–1099.
13. Meisheri KD, Khan SA, Martin JL. Vascular pharmacology of ATP-sensitive K$^+$ channels: Interactions between glyburide and K$^+$ channel openers. *Journal of Vascular Research* 1993; **30**. 2–12.
14. Lischke V, Busse R, Hecker M. Selective inhibition of barbiturates of the synthesis of endothelium-derived hyperpolarizing factor in the rabbit carotid artery. *British Journal of Pharmacology* 1995; **115**: 969–974.
15. Kessler P, Lischke V, Hecker M. Etomidate and thiopental inhibit the release of endothelium-derived hyperpolarizing factor in the human renal artery *Anesthesiology* 1996; **84**: 1485–1488.
16. Park WK, Lynch C III, Johns RA. Effects of propofol and thiopental in isolated rat aorta and pulmonary artery. *Anesthesiology* 1992; 77: 956–963.
17. Kitamura R, Kakuyama M, Nakamura K, Miyawaki I, Mori K. Thiobarbiturates suppress depolarization-induced contraction of vascular smooth muscle without suppression of calcium influx. *British Journal of Anaesthesia* 1996; 77: 503–507.
18. Chang KSK, Davis RF. Propofol produces endothelium-independent vasodilation and may act as a Ca^{2+} channel blocker. *Anesthesia and Analgesia* 1993; 76: 24–32
19. Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS. Pharmacokinetics of propofol (Diprivan) in elderly patients. *British Journal of Anaesthesia* 1988; **60**: 146–150.
20. Burch PG, Stanski DR. The role of metabolism and protein binding in thiopental anesthesia. *Anesthesiology* 1983; **58**: 146–152.
21. Morgan DJ, Blackman GL, Paull JD, Wolf LJ. Pharmacokinetics and plasma binding of thiopental. I: Studies in surgical patients. *Anesthesiology* 1981; 54: 468–473.
22. Servin F, Desmonts JM, Haberer JP, Cockshott ID, Plummer GF, Farinotti R. Pharmacokinetics and protein binding of propofol in patients with cirrhosis. *Anesthesiology* 1988; **69**: 887–891.
23. Piatt JH jr, Schiff SJ. High dose barbiturate therapy in neurosurgery and intensive care. *Neurosurgery* 1984; **15**: 427–444.
24. Newman MF, Murkin JM, Roach G, Croughwell ND, White WD, Clements FM, Reves JG, the CNS Subgroup of McSPI. Cerebral physiologic effects of burst suppression doses of propofol during nonpulsatile cardiopulmonary bypass. *Anesthesia and Analgesia* 1995; **81**: 452–457.
25. Garcia CE, Kilcoyne CM, Cardillo C, Cannon RO III, Quyyumi AA, Panza JA. Effect of copper–zinc superoxide dismutase on endothelium-dependent vasodilation in patients with essential hypertension. *Hypertension* 1995; **26**: 863–868.
26. Zuccarello M, Bonasso CL, Lewis AI, Sperelakis N, Rapoport RM. Relaxation of subarachnoid hemorrhage-induced spasm of rabbit basilar artery by the K$^+$ channel activator cromakalim. *Stroke* 1996; **27**: 311–316.

British Journal of Anaesthesia 1998; **81**: 771–781

REVIEW ARTICLE

Evoked responses in anaesthesia

C. THORNTON AND R. M. SHARPE

The aim of this review is first, to provide the clinical anaesthetist with a sufficient background regarding evoked responses, and second, to present current research in this sphere, thereby allowing an appraisal to be made of the usefulness of evoked potentials in the clinical setting. We shall consider: (1) the background, including the origins of the various evoked response components and the technical and subject related factors which should be considered when using evoked responses; (2) potential clinical applications: (a) as a monitor of awareness and depth of anaesthesia/sedation; and (b) for the assessment of nociception and pain.

Background

Evoked responses are derived from the electroencephalogram (EEG) in response to auditory, somatosensory, nociceptive and visual stimuli. These evoked responses are obvious candidates for investigation as they reflect the *functional integrity* of specific peripheral and central nervous system (CNS) regions in humans. The changes that occur in the evoked responses allow anaesthetists to assess the effects of the drugs that they are administering on the target site, namely the brain, *in vivo*. Consequently, interest in evoked response monitoring in the three speciality areas of clinical anaesthesia (general anaesthesia, intensive care and pain assessment), has increased considerably in the past 10–15 yr. This review explores the potential usefulness of evoked responses in fulfilling these aims, based on an understanding of the research in these areas.

PRODUCTION OF THE EVOKED RESPONSE

Many types of stimuli evoke a response in the EEG. To extract the response from background "noise", signal averaging is necessary to produce an "averaged" evoked response. Modern techniques digitalize EEG waveforms for a specified time after the stimuli and add them together. The response to the stimulus emerges and background noise which occurs randomly with respect to the stimulus is therefore cancelled out. These techniques require the stimulus to be applied at a known and precise point in time. This is straightforward for auditory, visual, electrical and laser stimuli, but less so for mechanical stimuli.

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Keywords: brain, evoked potential, monitoring, evoked potential; anaesthesia, depth; memory

ORIGINS OF THE EVOKED RESPONSE

Different evoked responses reflect different functional or anatomical areas of the brain. The auditory, somatosensory and laser evoked responses waveforms are shown in figures 1, 2 and 3, respectively.

The auditory evoked response (AER) waveform with its series of peaks and troughs represents the passage of electrical activity from cochlea to cortex. Figure 1 shows 11 waves generated by a sound stimulus given at the origin on a logarithmic scale. The brainstem waves represented by the Roman numerals I–V are generated from sites in the brainstem.[46 47 57] The early cortical (or middle latency waves) No, Po, Na, Pa, Nb are generated from the medial geniculate and primary auditory cortex.[50 90] The late cortical waves P1, N1, P2, N2 and P3 are generated from the frontal cortex and the association areas.[55 80]

Somatosensory evoked potentials (SEP) can be recorded by stimulating almost any nerve trunk at various levels. The most frequently studied are those in response to median and ulnar nerve stimulation. Constant current stimulation of the median nerve through a pair of surface electrodes strapped to the patient's wrist gives the responses generated by the fine touch somatosensory pathway (fig. 2). N13 is thought to originate from the dorsal column nucleus cuneatus,[56] N14 from the medial lemniscus,[1] and N20 and N35 from the region of the thalamus and primary cortex.[1 25 38] Subsequent waves probably originate from the frontal cortex and association cortices.

The SEP elicited in response to cutaneous painful stimuli have a longer latency depending on the site and type of stimulus. The nociceptive signal travels via small diameter myelinated A-delta and unmyelinated C-fibres to the dorsal horn via the dorsal root ganglion. Second order neurones relay the signal to the thalamus via the spinothalamic tract. Third order neurones project from the thalamus to the primary sensory cortex where the conscious perception of pain occurs.[16]

A "vertex potential"[3] is the SER associated with the sensation of pain and it is labelled according to polarity (P=positive and N=negative) and latency. Components with latencies at 100–700 ms are thought to coincide with secondary cortical processing involved in stimulus recognition and localization and with the magnitude and characterization of painfulness. These are called *late* components (fig. 3A) to distinguish them from the *ultra late* components (fig. 3B) which have latencies of 1–2 s.[2 15 43]

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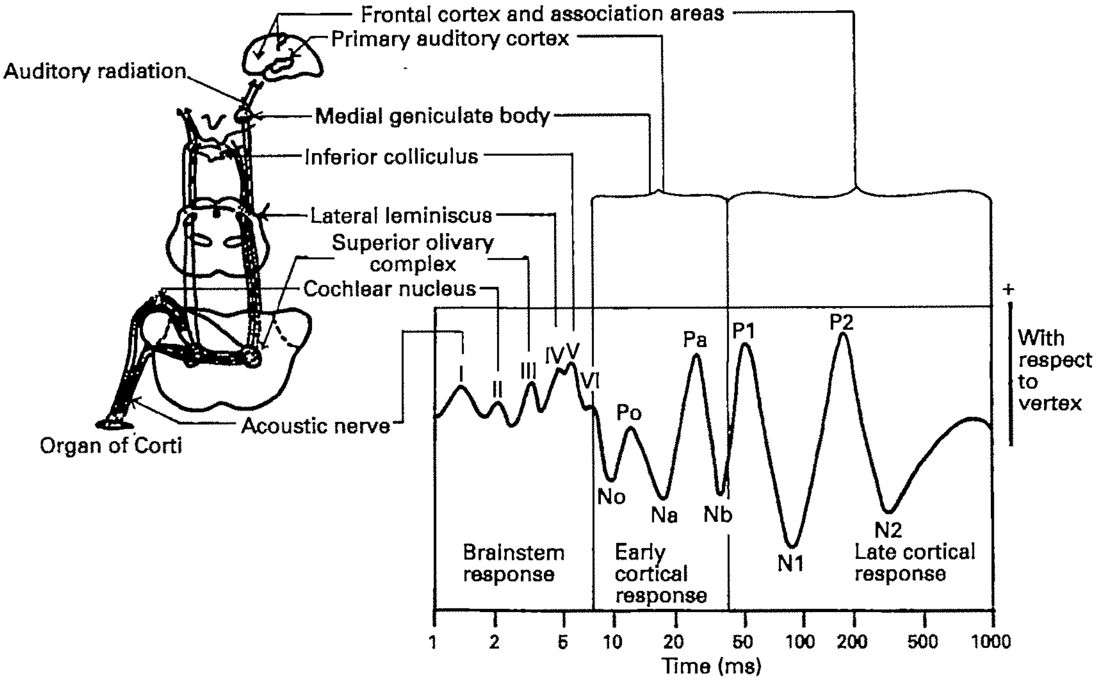

Figure 1 Auditory evoked response. This diagram describes the nomenclature of the response and shows its anatomical relationship with the auditory neuraxis. The brainstem response has a well documented anatomical relationship with the auditory neuraxis, whereas later responses have origins which are less easy to define.

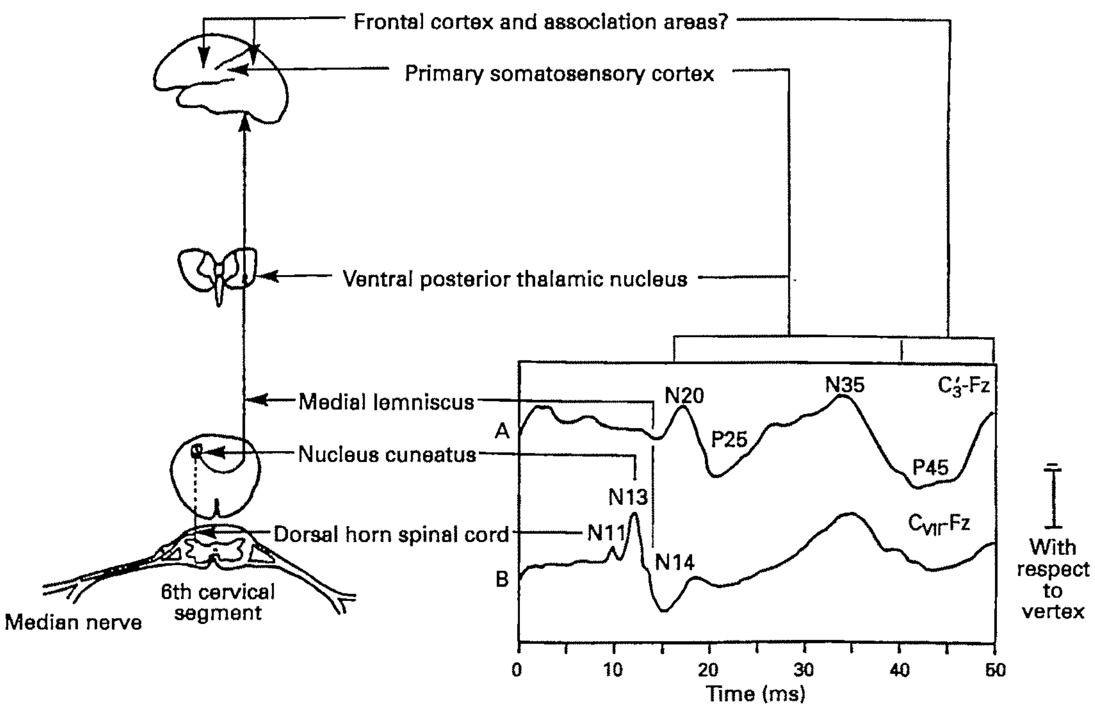

Figure 2 Somatosensory evoked response. This diagram shows waveforms obtained when the stimulating electrode is placed at the wrist above the median nerve and the recording electrodes are above (A) the somatosensory cortex and (B) the seventh vertebra. The nomenclature of the response and its anatomical relationship with the fine/touch somatosensory neuraxis is shown.

Visual evoked responses have been studied extensively by neurophysiologists, but little research exists with respect to anaesthesia.

EVOKED RESPONSE—TECHNICAL CONSIDERATIONS

Equipment for recording and analysing evoked responses

A system that can be used to record evoked responses is shown in figure 4. Developed at Northwick Park Hospital[49] specifically for use in the operating theatres, it consists of a small multichannel pre-amplifier, linked via an optical fibre cable to a personal computer (PC) fitted with a specially adapted digital signal processing board. This ultimately could fit into any multimode monitoring device. The EEG is recorded from scalp electrodes, amplified and relayed to the computer. The pre-amplifier also produces the stimulus, in the diagram an auditory stimulus, which is applied to the patient's ears via miniature earpieces. Software installed on the PC

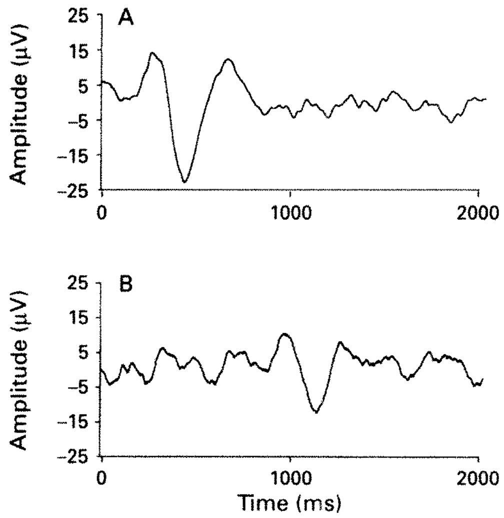

Figure 3 Argon laser-evoked vertex potentials, showing (A) the late potential, latency 430 ms and (B) a single sweep ultralate potential with a latency of 1150 ms.

analyses the EEG with respect to the stimulus to produce an averaged evoked response, which is constantly updated and displayed on the screen. There are a number of commercial evoked response systems available. Apart from the obvious features such as portability and ease of use, the equipment should be flexible in terms of filtering and analysis. For use in the operating theatres, good isolation against diathermy frequencies to prevent damage to the amplifiers and a low intrinsic noise level are required.

The following sections review briefly the technical details, such as electrode placement, stimulus type and repetition rate, how many responses should contribute to the average and what filtering should be applied? Many of the methodologies were developed previously by audiologists, neurologists and psychologists who were the first to use evoked response techniques routinely. These technical considerations and the factors affecting the evoked responses have been fully reviewed previously.[82]

Electrode placements

All evoked responses derived from the EEG described, are recorded from bipolar surface electrodes. In the case of the auditory evoked responses shown in figure 1 the electrical potential recorded from an electrode placed on the centre of the top of the head (reference or inactive electrode) is subtracted from that recorded from an electrode placed over the temporal lobe, on the mastoid process (active).

Some evoked responses can be recorded using an active electrode placed at a distance from the neural generator (farfield potentials). For example good brainstem and early cortical AER can be recorded from an active electrode placed over the inion process at the back of the head, some distance from the temporal lobe. This is useful in awake subjects as there is less interference from pre-auricular muscle tone. The late and ultra late potentials in response to nociceptive stimuli are recorded from the vertex (active) referred to linked mastoids.

Stimulus characteristics

Type of stimulus. The stimulus modality depends on the sensory pathway of interest (i.e. auditory, somatosensory, nociceptive or visual). Then the precise type of stimulus has to be chosen. Early cortical auditory evoked responses are best evoked by clicks of short duration (100–500 ms). For visual responses, a short flash of approximately 12 μs duration is often chosen.

Somatosensory stimuli (mechanical, electrical or laser) can be applied cutaneously, thus stimulating peripheral receptors of specific sensory modalities such as pain and touch. Alternatively, electrical stimuli can be applied more proximally by surface electrodes over a major nerve trunk. This stimulates all modalities (including motor and sensory) in the trunk depending on the duration and intensity of the stimulus.

In pain studies using evoked potentials there is much discussion as to the suitability of stimuli. Ideally a stimulus should be: (1) exclusively painful (i.e. touch, pressure receptors, should not be triggered by non-painful stimuli); (2) quantifiable in terms of the intensity and duration; (3) easily applied, removed and repeated without generating tissue damage. Habituation to the response should not occur.

Electrical stimuli have been used extensively in pain research as they are easy to apply, quantify and repeat. However, the stimulus is unnatural and the strong electrical current required to produce pain

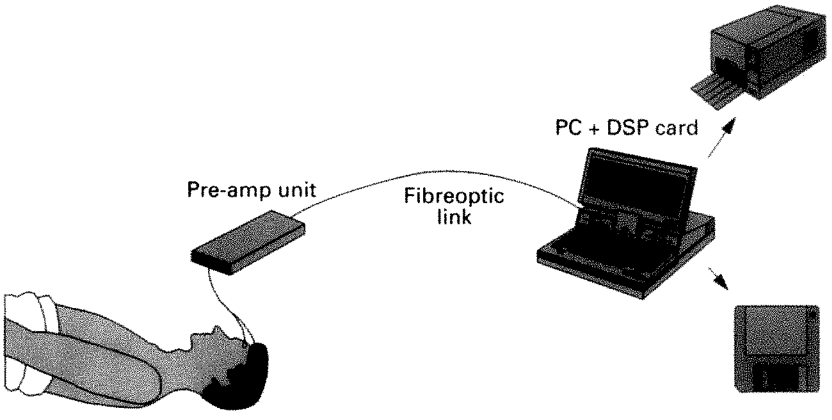

Figure 4 Recording evoked responses. The system developed at Northwick Park Hospital consists of a small multichannel pre-amplifier, linked via a fibreoptic cable to a personal computer (PC). The stimulus (in this case clicks) are generated by the pre-amplifier and presented to the patient through miniature ear-pieces.

stimulates different nerve types, including motor (A-alpha) and mixed sensory (A-beta) nerves. Thus in addition to the pain, the subject may experience twitching, tapping and tingling. Attempts have been made to modify the electrical stimulus by removing a small core of epidermis from the skin on the pulp of the finger.[14] We have used fine intradermal acupuncture needles to deliver electrical stimuli, again the stimulus is not purely nociceptive (personal observation).

Thermal stimulation elicits a sensation that is considered more "natural".[26] Many different methods have been used, but only laser emitted radiation is useful for producing pain evoked potentials. The technique produces a painful stimulus with a relatively short duration (10 ms) that is readily "time-locked" to the EEG. Additionally, the stimulus intensity is easily quantified and varied allowing the determination of "laser pain thresholds" (the least stimulus intensity at which the subject perceives pain).

Stimulus intensity. A certain level of stimulus is required to elicit a response. Between this threshold, up to a certain point, increasing the intensity of the stimulus increases the amplitude of the response and decreases latency. The stimulus intensity may be set in relation to an individual's threshold, such as is the case for the median nerve somatosensory evoked response, where the electrical stimulus is usually fixed at 1.5 times the motor twitch threshold which ensures a supramaximal sensory stimulus. Electrical and laser stimuli are easily adjusted and quantified. For the auditory and visual evoked responses the stimulus is often set at a fixed intensity above the population's average threshold.

Stimulus presentation rate. This is important clinically, as increasing the rate of stimulus presentation can reduce the time taken to carry out the test. The number of stimuli needed to produce a clear averaged response depends on the amplitude of the response in relation to the background noise. However, increasing the stimulus presentation rate above a certain value can in itself reduce response as a result of stimuli being presented within the refractory period of the previous response and as a result of response overlapping. When responses overlap, deflections of opposite polarity occur together and the amplitude of the average is reduced. Under normal circumstances a compromise has to be reached between the clarity of the response and the time taken to obtain it. Short latency waves of the auditory (early cortical) and somatosensory evoked responses can be produced by fast stimulation rates. Usually 512–1024 sweeps are averaged, representing 1–2 min of data collection at a stimulus rate of 6 Hz. Some workers find it beneficial to use irregular stimulus repetition rates to desynchronize the response from regular sources of interference such as EEG and 50-Hz mains signals.

Side of stimulation. For all three modalities, the sensory pathways cross over in the spinal cord or brain so that the side of stimulation affects the response. This lateralization of the response has been exploited to deduce the anatomical origins of the waves. After crossing over has occurred the precise location of the generators influence whether the waves are the same size or larger on the contralateral side. Stimulation from both, as opposed to one side of the body, increases wave amplitude and decreases wave latency.

Analysing the evoked response

The latencies of the peaks and troughs (in ms) along the horizontal axis and their amplitude (μV) along the vertical axis may be measured manually. This is the simplest method by which changes in evoked responses can be assessed and a valuable contribution has been made from data collected in this way.

Power spectral analysis (based on fast Fourier transformations) of the evoked response waveform has been applied by Schwender and colleagues.[72] Coherent frequency analysis may be applied to the steady state evoked response.[60] We have described an index based on the average second differential of the waveform for a time window which includes the early cortical response.[87] Doi and colleagues prefer the sum of square root of absolute difference between any two successive 0.56-ms segments of the AER waveform.[32] A novel attempt has been made by Stockmanns and colleagues[78] to derive numerical indices from evoked responses using the technique of wavelet transformation. The AER waveform is decomposed into constituent waveforms using one specific function—there are a number of known wavelet transformation functions. This approach differs from fast Fourier transformation, which is based on cosine and sine functions only. These sophisticated methods of analysis have the advantages that they are objective and can be automated but they do not necessarily provide additional or better information than the manual methods.

Filtering

To allow comparison of amplitude and latency, uniform filtering must be applied to every subject in each study (and between studies if comparisons are to be made). Some filtering of the EEG, before signal averaging and of the averaged evoked response waveform itself, can be useful. It serves to abolish frequencies which interfere with the interpretation of the waveform. Appropriate filtering can make the waveforms between runs and between subjects more reproducible but when it is too severe, it may attenuate the response of interest or even abolish it completely.[51] Digital filtering is preferable to analogue filtering as the latter can change latency and distort the signal. A compromise has to be reached, bearing in mind that both the frequency content of signal and noise may be changed by the effect or treatment studied. For instance, the dominant frequencies in children's early cortical AER are shorter than in adults requiring adjustments in filtering. The AER of children less than 2 yr of age are also more susceptible to interference from ECG, which in combination with certain filter ranges can give rise to misleading data.[63]

EVOKED RESPONSES—SUBJECT RELATED CONSIDERATIONS

Factors related to the subjects studied may influence the evoked response obtained. Consideration of these factors is necessary when potentials are compared between different individuals and studies.

Temperature

In general, hypothermia produces an increase in latency and may also produce a reduction in amplitude, depending on the severity of the decrease in temperature.[44] Hyperthermia has the opposite effect.[12] The somatosensory evoked response is the most susceptible to changes in temperature, as a major section of the pathway is peripheral. Skin temperature influences sensory and pain thresholds elicited by laser stimulation.[4]

Skin characteristics

Skin thickness and reflectance (colour) can also influence the amount of laser energy in the vicinity of the nociceptor.[4]

Age and sex

There is much discussion on the effects of age and sex on the evoked responses, which may suggest that the effects are not large compared with the population variability and therefore can largely be discounted with respect to anaesthesia and ITU monitoring. The general trend for all responses is an increase in latency with age. Differences in amplitude may relate more to skull size than to age or sex. In some cases the elderly are less sensitive to laser stimuli, reductions in amplitude with increased latency were observed with increasing age.[37]

Natural sleep and level of arousal

The waves of the auditory evoked response before 30 ms (Pa) appear stable to changes in the level of arousal (i.e. sleep, level of alertness). Later waves change dramatically during sleep. Pb/P1 completely disappears during deep (stages 3 and 4) natural sleep.[33] It is this aspect which has been exploited to measure potential awareness during anaesthesia. In awake subjects, increased amplitudes of the late cortical responses have been shown to be associated with higher levels of alertness/attention.[65]

The effects of arousal or natural sleep on the visual or somatosensory evoked responses have not been studied extensively, probably because of the obtrusiveness of these stimuli.

Neurological disease

Many of the original applications of evoked responses were for the diagnosis of neurological diseases. Peripheral lesions affect the evoked responses and have to be considered if the evoked responses are used to monitor depth of anaesthesia or to assess pain.

The visual evoked response, for example, is affected by lens defects such as cataract[81] and conditions such as optic neuritis.[41] The auditory evoked responses are affected by conductive and sensorineural hearing disorders[34] and somatosensory evoked responses by damage to sensory nerves and nerve roots.[36] Multiple sclerosis and other demyelinating diseases can affect the response.[25 42 66] Demyelinating diseases have a selective action on A-delta fibres leaving the unmyelinated C-fibres intact. This may result in an absent late vertex potential with the emergence of an ultra late response thought to be transmitted via C-fibres.[16]

Tumours, which affect the specific nerve tracts,[57] and factors which affect the brain, such as ischaemia[67] and coma[38 45 77] can also affect evoked responses.

Monitoring awareness, depth of anaesthesia and sedation

CLINICAL REQUIREMENT

After the introduction of neuromuscular blocking drugs, many of the traditional signs of anaesthesia were rendered useless and intraoperative awareness during general anaesthesia emerged as a problem. This prompted the search for methods for detecting awareness during anaesthesia and the graded changes that occur in the CNS related to depth of anaesthesia. The anaesthetist requires a monitor of anaesthetic depth, they are then able to react to prevent awareness and tailor the dose of the drug to the patient's requirements. Prompt emergence from anaesthesia or sedation is then possible if required. Another useful application of such a monitor would be to predict if a patient was going to move in response to or during surgery in spontaneously breathing patients. A monitor of awareness could be beneficial in the ITU situation, especially in sedated patients with whom it is difficult to communicate.

The EEG has been known for some time to show graded changes with increasing concentration of inhalation anaesthetics.[28 35] Generated from within the CNS, the EEG is not affected by neuromuscular blocking agents. Attention was therefore directed towards the EEG as a possible indicator of awareness and depth of anaesthesia. However, extensive research has proved disappointing as the EEG changes seen with general anaesthetics vary for different agents.[27] The evoked responses were the next candidates for investigation. In the studies reviewed below, motor responses and psychological tests of implicit and explicit memory have been used to assess awareness and attempts have been made to correlate evoked responses with these variables.

RESEARCH EVALUATING USE OF EVOKED RESPONSES

To detect awareness during anaesthesia

Certain definitions are important for interpreting research findings. In a patient who is aware during anaesthesia, memory can be explicit or implicit. Explicit memory occurs when the patient/subject is able to recall events happening during surgery or words spoken during an experiment. Implicit memory occurs when the patient/subject's behaviour is modified by information given during "anaesthesia", but they have no direct recollection of the event.

To date, the early cortical auditory evoked response is the most promising of the evoked response for distinguishing a patient who is aware from one who is anaesthetized. A positive response to verbal command and in some cases recall has been shown to be associated with an Nb latency <44.5 ms (the mean value from a discriminant function analysis).[83] This value is taken as it represents the transition between a "three-wave trace" (danger of awareness) and a "two-wave trace" (fig. 5). Using an isolated forearm technique, seven patients were studied before surgery. Anaesthesia was maintained with 70% nitrous oxide in oxygen. Every 2–3 min the patient was asked to squeeze the fingers and then let go of the investigator's hand, the AER was studied before and after this command. If no response occurred, nitrous oxide was reduced slowly to 50% or until a clear response was seen. An unambiguous endpoint was taken when the patient gave a positive response after a period of "no response". This happened in four of seven patients and was correlated with a short (<44.5 ms) Nb latency. None of the patients had explicit memory of events. Implicit memory was not tested.[83]

In another study, volunteer anaesthetists were given sub-MAC concentrations of isoflurane (0, 0.1, 0.2 and 0.4 MAC) on 4 separate days.[62] During a period when end-expiratory isoflurane was steady, psychological tests were carried out in which the subjects were given simple or complex commands (e.g. raise your left hand) and a list of words to memorize. The AER was recorded throughout. At 0 MAC all subjects had explicit memory of the commands and remembered being asked to memorize words, at 0.4 MAC none of the subjects followed commands and had no recollection of the proceedings. (Implicit memory was not tested.) At the intermediate MAC levels there was incomplete reduction of function in some subjects. A correlation between Nb latency and response to command was demonstrated in seven of eight subjects.

In further studies, loss of verbal response to command and eyelash reflex after a bolus dose of midazolam was associated with an increase in Nb latency from 44 to 58 ms[89] and after midazolam and propofol infusion with an increase from 44.3 to 55 ms.[61] The association between Nb latency and awareness has been confirmed by other investigators who have studied the transition from consciousness to unconsciousness. Davies and colleagues[30] used a target-controlled propofol infusion to produce two clinical states which they defined as (1) "conscious" where the patient responded to verbal command and (2) "unconsciousness" where no response to verbal command occurred and the eyelash reflex was lost. Comparison of the AER was made between each state. In this study both Pa and Nb latency were able to discriminate between the two states and were statistically significant in all transitions. Several other workers found Nb latency to be the best correlate, out of a group of EEG variables, with loss of eyelash reflex[88] after propofol sedation and subsequent arousal after physiotherapy.[76]

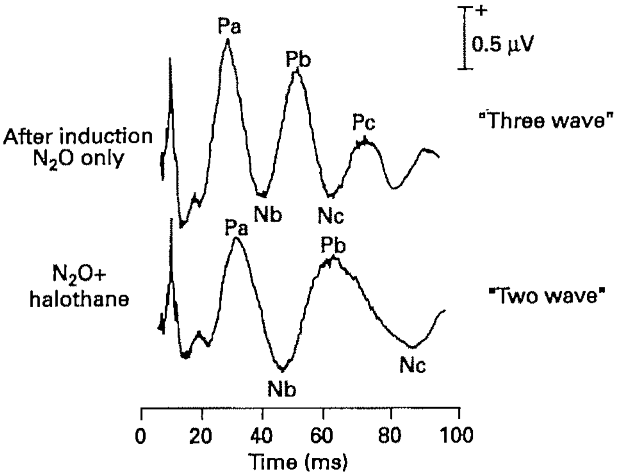

Figure 5 Early cortical response. Top: the three positive waves, Pa, Pb and Pc, with latencies of 15–100 ms, suggest light anaesthesia/potential awareness At this time anaesthesia was maintained with 70% nitrous oxide in oxygen. Bottom: after addition of a small amount of halothane, the three waves were replaced by two positive waves, Pa and Pb, suggesting no awareness.

From reports of intraoperative awareness, using a variety of anaesthetic techniques, it is often noted that the auditory input is the last sensory modality to be abolished[23 39 48] and the first to return at light levels of anaesthesia. Patients anaesthetized for cardiac surgery are often studied, as a high incidence of awareness has been reported.[40 59] For example, Schwender and colleagues studied 45 patients undergoing cardiac surgery.[71] Anaesthesia was maintained with high-dose fentanyl (1.2 mg h^{-1}), supplemented with flunitrazepam 1.2 mg h^{-1}, 0.6–1.2% isoflurane, propofol 4–8 mg kg^{-1} h^{-1} or no additional agent (control group). After sternotomy, patients were played a tape message with an implicit memory task. The AER was recorded throughout. No patient experienced explicit memory of intraoperative events, but seven patients showed implicit memory related to the tape message. A correlation with the AER, in particular Pa latency, was demonstrated. Nine patients demonstrated a shift in Pa latency of <12 ms; these included all seven patients with implicit memory. Of the remaining 23 patients, without implicit memory changes, 21 had a Pa latency shift of >12 ms.

Generally, the amplitudes of the Pa and Nb waves are preserved during sedation with benzodiazepines.[73] As the generators of the early cortical AER are located in the primary auditory cortex and temporal lobe, this suggests that the benzodiazepines do not completely suppress cortical processing of auditory stimuli. This may have some relevance to reports of intraoperative awareness during anaesthetic techniques using benzodiazepines.[73] There is also evidence to suggest that other sensory modalities are not completely suppressed by benzodiazepines. For example there is little or no change in the amplitudes and latencies of visually evoked potentials (VEP) after administration of diazepam.[54] Changes in the SER have been demonstrated with benzodiazepines. A 60% depression of the amplitude of the cortical SSEP was demonstrated with midazolam, and small but significant reductions in latency were seen.[75]

Changes in Nb and Pa latency and derived indices which reflect these changes appear to be the best discriminators of aware and anaesthetized. An obvious application is to devise a feedback loop to control sedation at a comfortable level for the patient.[68] This could then be applied to patients in the ITU in whom it is impossible to determine adequate sedation with existing clinical tests.

To measure "depth of anaesthesia"

The early cortical AER also been investigated systematically at the deeper levels of anaesthesia.[69 74 86] It shows graded changes with the general anaesthetics halothane, enflurane, isoflurane, desflurane, sevoflurane, propofol, etomidate and Althesin and these are partially reversed by surgical stimulation, as would be expected of the changes which were monitoring "depth of anaesthesia" as opposed to concentration.

Figure 6 shows the effect of desflurane on the early cortical AER. Pa and Nb amplitudes flatten and their latencies lengthen, from a high amplitude wave at 1.5% to virtually a flat line at 6.0% end-tidal desflurane.

The brainstem waves, although showing graded changes with inhalation anaesthetics, were not affected by i.v. agents over the clinical concentration range[86] and therefore have been discounted. Late cortical waves are too sensitive and are completely abolished by sedative doses of these agents.

The effect of surgical stimuli such as first incision[85] and tracheal intubation[17] have been examined on these graded changes in the AER and shown to partially reverse them. For example, applying a stimulus when the patient is maintained with a constant anaesthetic concentration causes the AER to change to one that is associated with a lower concentration of anaesthetic (or lightening of anaesthetic depth). The effect of tracheal intubation on the AER is shown in figure 7. After intubation the latencies of Pa and Nb shorten and the amplitudes increase.

The later waves of the somatosensory evoked responses, P35/N45, show similar changes with anaesthesia to the AER. However, the electrical pulse is not as acceptable to patients as a click and the recording electrodes have to be attached to the hairy parts of the scalp at precisely measured points. This makes the system less viable as a routine clinical monitor. Good early cortical AER recordings can be made in anaesthetized patients from ECG adhesive electrodes attached at the mastoid and forehead. Another problem with the SER is that the amplitudes of the waves are very variable between patients and therefore changes in the response caused by anaesthetics would have to be compared against a "non-anaesthetized" baseline. This does not appear to be necessary for the AER. Nevertheless, the SER has proved useful as a research tool. When the SER has been studied over a range of concentrations of various anaesthetic agents, the amplitudes of the later waves (P35 and N35) behaved similarly to Pa and Nb of the AER, in that they are not particularly sensitive to analgesics such as nitrous oxide but are profoundly affected by agents such as isoflurane. These changes are reversed to some extent by tracheal intubation.[29]

The visual evoked response has received little attention as a measure of depth of anaesthesia. It merits further investigation, possibly using goggles to give flash stimuli through closed eyelids.

To predict movement to surgical stimulation

The effect shown by both early cortical auditory and somatosensory responses after tracheal intubation and surgical stimulation suggest that these responses reflect the balance in the CNS between the depressant effects of anaesthesia and sensory stimulation and are not simply monitors of anaesthetic concentration. However, the evoked responses have not emerged as reliable predictors of whether an individual patient will move during anaesthesia. For instance, a recent study by Schwender and colleagues investigated patients undergoing elective gynaecological laparotomy under midazolam "anaesthesia" with analgesia provided by continuous epidural.[70] During the study, a total of 25 movements were observed (10 spontaneously and 15 in response to verbal stimuli—"open your eyes"). After induction the only significant change in the AER was prolongation of Nb latency. There was no significant change in the AER before and during intraoperative movements compared with AER recordings when no movement occurred. There was no predictive value of the early cortical AER for whether or not the patient would move during anaesthesia.

The same conclusion was reached in a multicentre European study where 82 patients were investigated to determine if the response in the AER to a tetanic stimulus could predict if the patient would move to surgical incision.[52] None of the AER measurements made before incision predicted whether or not patients subsequently moved.

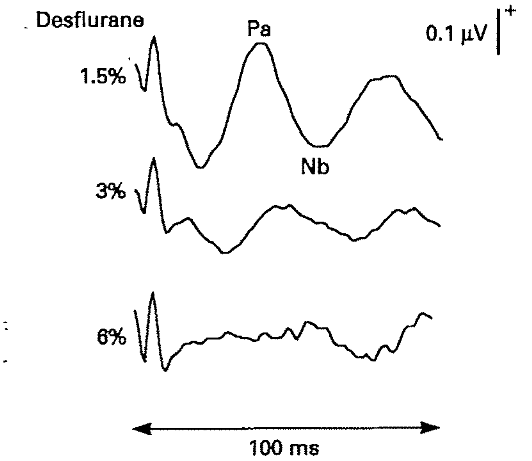

Figure 6 Early cortical auditory evoked responses in a patient receiving desflurane and 67% nitrous oxide in oxygen. Latency increases and amplitude decreases with increasing concentration.

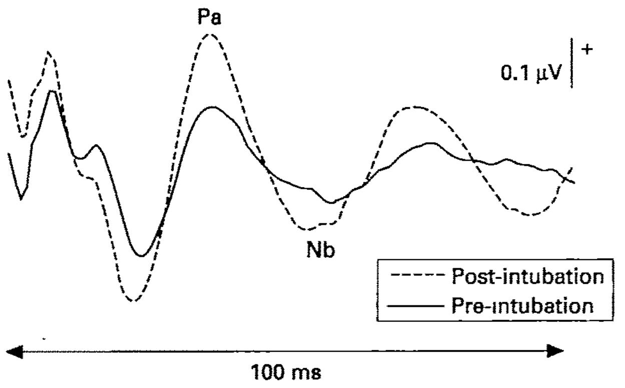

Figure 7 Early cortical auditory evoked response before and after intubation. Pa and Nb amplitudes increase and amplitudes shorten after this strong sensory stimulus, even though the anaesthetic concentrations were constant throughout.

Assessment of pain

CLINICAL REQUIREMENT

Most human pain research using evoked responses has been carried out in awake subjects. The late and ultra late potentials evoked by laser stimulation are the most promising for pain assessment.

Carbon dioxide[58] and argon lasers[11] have been used in the study of pain. The use of infra-red carbon dioxide laser causes a rapid increase in skin temperature[20] resulting in superficial skin lesions,[10] making this stimulus less suitable for repetitive stimulation. The local inflammation that it produces also modifies the nociceptive pathway. The visible argon laser stimulus does not produce these effects and can be applied via quartz fibre for cutaneous stimulation.[4]

The exact mechanism of pain generation by laser stimulation is unknown, but it is generally assumed that the laser heat stimulates warmth and polymodal nociceptors located intradermally.[13] As the intensity of the laser stimulus is increased, various sensations are produced (personal observation). Ranging from: (1) no sensation; (2) a slight tingling feeling (not painful) sometimes labelled "pre-pain"; (3) a definite pinprick (first pain); and (4) a delayed burning pain (second pain) usually preceded by a pinprick.

An effective method of assessing pain with evoked potentials should show graded change with pain intensity and the response to the pain stimulus should be obtunded by analgesic medication. The next section reviews the literature with these requirements in mind.

RESEARCH EVALUATING USE OF EVOKED RESPONSES

Are there graded changes with stimulus intensity?

The majority of pain studies using evoked responses have studied the late component of the vertex potential, thought to be mediated via A-delta fibres. A linear relationship between the amplitude of the vertex SEP and pain perception has been demonstrated with electrical[18 21] and laser stimulation.[11 19 79]

Is the response to pain stimulus obtunded by analgesic medication?

Opioids. Several studies[7 18 21] have shown that the amplitude of pain-evoked vertex potentials was reduced by opioids. For example, i.m. alfentanil reduced the amplitude of the laser evoked response and increased pain thresholds by 116% while sensory thresholds (warmth) were unchanged.[7] These effects were reversed by naloxone 400 µg. Sensory thresholds were not significantly affected by alfentanil, suggesting a pure analgesic effect. In this study there was no significant effect on the latency of the evoked response, despite an increase in the reaction time of the subjects (who pressed a button when they experienced the pinprick). The differences were attributed to the complex central depressant actions of opioids on arousal/attention rather than a direct nociceptive effect. This led to the criticism that central opioid action on arousal is responsible in part for the effect on the evoked response—this is discussed later.

Local anaesthetics. Studies on topical, perineural and epidural local anaesthetics support the vertex potential as a measure of pain sensation. For example, changes in the amplitude and latency of the laser evoked cortical responses reflected changes in perception of pain when the local anaesthetic EMLA cream was applied.[5 79]

The amplitude of the vertex potential elicited by argon laser stimulation was reduced by 42% after administration of the local anaesthetic bupivacaine into the epidural space at L2–3.[8] A differential effect was seen at the outer dermatomal limits of the epidural. In the caudal segments, different effects on warmth (sensory) and pain (pinprick) thresholds were seen. This could be attributed to the differential effect of low concentrations of local anaesthetic on the A-delta and C-fibres. Administration of epidural morphine produces similar reductions in amplitudes together with increased pain thresholds for up to 7 h. The changes were antagonized by naloxone. No change in the latency of the evoked response was seen.[9]

Oral analgesics and non-steroidal anti-inflammatory drugs. Studies have demonstrated a 20–35% reduction in the amplitude of the evoked response to electrical and laser nociceptive dental stimuli after administration of aspirin.[24 31] Reductions in the amplitude of the SEP produced by paracetamol and paracetamol–codeine combinations were also demonstrated in a placebo-controlled crossover study. For both drugs, the pinprick threshold was increased maximally at 2 h. Similarly, the evoked response was reduced maximally at 2 h for paracetamol alone but at 1 h for paracetamol–codeine. The evoked response did not mirror completely the changes in pain threshold.[6]

So far the ultra late vertex potential has only been elicited to acute painful electrical[43] as well as carbon dioxide[15] and argon laser[2] stimuli. It may find a place in chronic pain research as a neurophysiological correlate of C-fibre activity.[26] (Evoked responses have not yet found a role in the study of chronic pain which is thought to be modulated by C-fibres.) The ultra late potential can be elicited if a pressure block can be applied over the afferent nerve pathway which blocks the A-delta and leaves the unmyelinated C-fibres intact. In this situation the burning sensation predominates. It has been postulated that this reflects cortical processing from afferent C-fibre input because the timing of the ultra late potential (latency 1–2 s) correlates with the delayed burning sensation (so called second pain). Additionally, the difference in latency between the late and ultra late evoked potentials correlates with the different conduction velocities of the A-delta and C-fibres.

Nociception during anaesthesia

CLINICAL REQUIREMENT

Clinically we know that analgesic drugs such as opioids, nitrous oxide and NSAID obtund the pain response to surgery and reduce anaesthetic requirements. The extent to which they obtund the autonomic responses to surgery can be used as a measure of their analgesic efficacy. There have been several studies observing the changes in evoked responses to tracheal intubation and surgical stimulation and attenuation of these responses by opioids and nitrous oxide.[17 84 85] The results of these studies have led to claims that certain aspects of evoked responses, specifically the pontine thalamic components of the somatosensory evoked response can measure the analgesic component of balanced anaesthesia.

RESEARCH EVALUATING USEFULNESS OF EVOKED RESPONSES

In studies where patients were given either nitrous oxide or isoflurane the pontine–thalamic wave (P15–N20) was profoundly depressed with nitrous oxide (fig. 8). The cortical SER waves (P35–N45) and AER waves (Pa and Nb) were more depressed by isoflurane than nitrous oxide.[53 84]

Dose-related attenuation of the pontine–thalamic wave amplitude in response to intubation with remifentanil has been demonstrated.[29] As the pons–thalamus is the likely site of opioid receptors it was speculated that these waves reflect the analgesic aspects of anaesthesia. Attenuation of the Pa amplitude response to intubation with alfentanil[17] and a direct effect on Pa amplitude of both alfentanil[17] and remifentanil[29] have been demonstrated. The position with respect to the AER waves Pa and Nb and opioids is more controversial as there are no known opioid receptors in the auditory nerve pathway.

Areas of controversy

AWARENESS, DEPTH OF ANAESTHESIA, SEDATION AND THE AER

The early cortical AER would be a suitable basis as a method which detects intraoperative "awareness" as indicated by the patient's ability to register sound. If intra-operative awareness has to include subsequent memory (implicit or explicit) and some anaesthetists insist that it does, then the situation becomes more complicated because of the amnesic drugs used during general anaesthesia. A brain signal recorded at one point in time will not necessarily predict future behaviour accurately if events or treatments which occur in the period in between the two time points can influence behaviour. Precise definitions are necessary for understanding the research findings but these may not be as relevant to everyday clinical practice as clinical practitioners do not need to operate in borderline areas where small changes in anaesthetic depth could result in the difference between implicit or explicit memory.

Predicting movement after incision from pre-incision data has similar problems in predicting awareness. Also movements are affected by classes of drugs such as opioids, neuromuscular blocking agents, etc., which do not affect cortical activity directly. Any relationship between a spinal reflex, such as movement to surgical incision, and the cortical AER is likely to be very indirect, which may explain why the AER has such low prediction value.

PAIN ASSESSMENT AND THE SER

In general there is a relationship between the amplitude of the evoked response and the pain threshold (fig. 9).[5] Although there are occasions when dissociation occurs.[6]

It can be argued that the amplitude of laser induced vertex potentials are affected by the sedative actions of opioid analgesics and this accounts for the discrepancy between changes in the amplitudes and pain ratings. To try and separate sedative and analgesic actions, the effects of sub-anaesthetic doses of propofol and analgesic doses of alfentanil were studied on noxious stimuli.[64] Both propofol and alfentanil induced similar reductions in the amplitudes of the evoked potentials elicited by nociceptive and non-nociceptive (auditory) stimuli, but only alfentanil reduced perceived pain, indicating that the reduction in amplitude of the vertex potential by propofol was not caused by an analgesic effect.

Conclusion

Evoked responses are extracted from the background electrical and electrophysiological noise of the EEG. The early cortical AER waves Pa and Nb, which occur between 20 and 80 ms reflect the activity in the temporal lobe/primary cortex, the site of sound registration. Changes in the latency of these waves are highly correlated with a transition from awake to loss of consciousness and subsequent decreases and increases in the amplitude of these waves reflect the interplay of general anaesthetics, surgical stimulation and obtunding of the latter by analgesics. The early cortical AER

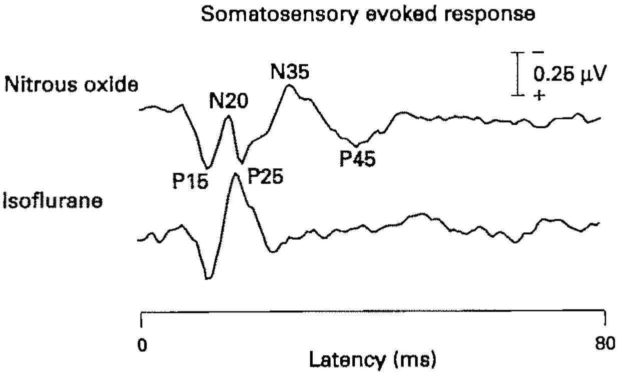

Figure 8 Changes in the somatosensory evoked response recorded from scalp electrodes and produced by stimulating the median nerve. The patient was given nitrous oxide or isoflurane. During the isoflurane period, P15–N20 and N20–P25 increased, and P25–N35 and N35–P45 were reduced compared with the nitrous oxide period.

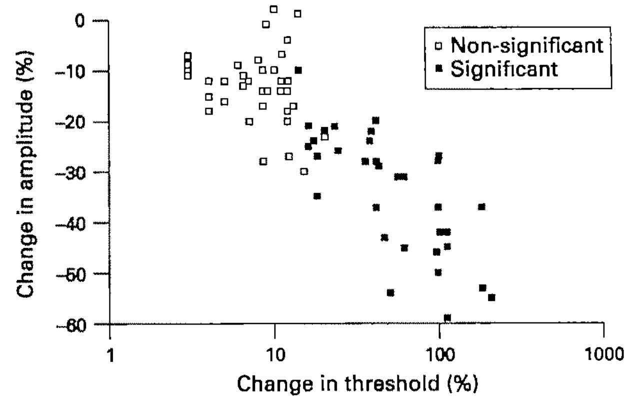

Figure 9 Changes in the distinct pinprick threshold (mean percentage change compared with baseline) compared with the corresponding change in amplitude (mean percentage change compared with baseline) of the argon laser-evoked vertex potential. Reproduced with permission from L. Arendt-Nielsen, *Acta Anaesthesiologica Scandinavica*, 1994.[5]

has real value in distinguishing between the aware and anaesthetized state and subsequent CNS depression. This would be useful in ensuring paralysed anaesthetized patients are unconscious or to control sedation during ITU or endoscopic procedures.

The laser pain evoked response shows great promise as an objective measure of pain. So far only the late vertex potential or A-delta fibre response can be detected reliably. There is much scope for further research using the ultra late vertex potential as a possible correlate of C-fibre activation. This could have enormous clinical application in chronic pain states.

Accepting some technical and subject related limitations outlined in the first part of this review, these two areas of evoked response monitoring have promising applications in the areas of general anaesthesia, intensive care and pain assessment.

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References

1. Abbruzzesse M, Favale E, Leandri M, Ratto S. New subcortical components of the cerebral somatosensory evoked potential in man. *Acta Neurologica Scandinavica* 1978; 58: 325–332
2. Arendt-Nielsen L. Second pain event related potentials to argon laser stimuli: recording and quantification. *Journal of Neurology, Neurosurgery and Psychiatry* 1990; 53: 405–410.
3. Arendt-Nielsen L. Characteristics, detection, and modulation of laser-evoked vertex potentials. *Acta Anaesthesiologica Scandinavica* 1994; 38 (Suppl. 101).
4. Arendt-Nielsen L, Bjerring P. Sensory and pain threshold characteristics to laser stimuli. *Journal of Neurology, Neurosurgery and Psychiatry* 1988; 51: 35–42.
5. Arendt-Nielsen L, Bjerring P. Laser-induced pain for evaluation of local analgesia A comparison of topical evaluation (EMLA) and local injection (Lidocaine). *Anesthesia and Analgesia* 1988; 67: 115–123.
6. Arendt-Nielsen L, Nielsen JC, Bjerring P. Double-blind, placebo controlled comparison of paracetamol and paracetamol plus codeine—a quantitative evaluation by laser induced pain. *European Journal of Pharmacology* 1991; 40: 241–247.
7. Arendt-Nielsen L, Oberg B, Bjerring P. Analgesic efficacy of i.m. alfentanil. *British Journal of Anaesthesia* 1990; 65: 164–168.
8. Arendt-Nielsen L, Oberg B, Bjerring P. Quantitative assessment of extradural bupivacaine analgesia. *British Journal of Anaesthesia* 1990; 65: 633–638.
9. Arendt-Nielsen L, Oberg B, Bjerring P. Hypoalgesia following epidural morphine: a controlled quantitative experimental study. *Acta Anaesthesiologica Scandinavica* 1991; 35: 430–435
10. Bjerring P. Quantitative monitoring of acute experimental cutaneous pain and inflammatory vascular reactions. *Acta Dermato-Venereologica* 1991; 71: 12–16.
11. Bjerring P, Arendt-Nielsen L. Argon laser induced single cortical responses: a new method to quantify pre-pain and pain perceptions. *Journal of Neurology, Neurosurgery and Psychiatry* 1988; 51: 43–49.
12. Bridger MWM, Graham JM. The influence of raised body temperature on auditory evoked brainstem responses. *Clinical Otolaryngology* 1985; 10: 195–199.
13. Bromm B, Jahnke MT, Treede RD. Responses of human cutaneous afferents to CO_2 laser stimuli causing pain. *Experimental Brain Research* 1984; 55: 158–166.
14. Bromm B, Meier W. The intracutaneous stimulus: A new pain model for algesimetric studies. *Methods and Findings in Experimental Clinical Pharmacology* 1984; 6: 405–410.
15. Bromm B, Treede RD Pain related cerebral potentials: Late and ultralate components. *International Journal of Neuroscience* 1987; 33: 15–23.
16. Bromm B, Treede RD. Laser-evoked cerebral potentials in the assessment of cutaneous pain sensitivity in normal subjects and patients. *Revue Neurologique (Paris)* 1991; 147: 625–643.
17. Brunner MD, Crabb JI, Millett SV, Thornton C, Newton DEF. Alfentanil obtunds the increase in the Pa amplitude associated with intubation in a dose dependent fashion. *Anesthesiology* 1995; 83: A301.
18. Buchsbaum MS, Davis GC, Coppola R, Naber D. Opiate pharmacology and individual differences. II. Somatosensory evoked potentials. *Pain* 1981; 10: 367–377.
19. Carmon A, Friedman Y, Coger R, Kenton B. Single trial analysis of evoked potentials to noxious thermal stimulation in man *Pain* 1980; 8: 21–32.
20. Carmon A, Mor J, Goldberg J. Evoked cerebral responses to noxious thermal stimuli in humans. *Experimental Brain Research* 1976, 25: 103–107.
21. Chapman RC, Colpitts YM, Benedetti C, Butler S. Event-related potential correlates of analgesia: Comparison of fentanyl, acupuncture and nitrous oxide. *Pain* 1982; 14: 327–337.
22. Chatrain GE, Canfield RC, Knauss TA, Lettrch E. Cerebral responses to electrical tooth pulp stimulation in man. *Neurology* 1975; 25: 745–757.
23. Cheek DB. The anaesthetized patient can hear and can remember. *American Journal of Proctology* 1962; 13: 287–290.
24. Chen ACN, Chapman CR. Aspirin analgesia evaluated by event-related potentials in man: Possible central action in brain *Experimental Brain Research* 1980; 39: 359–364.
25. Chiappa KH Short latency somatosensory evoked responses: interpretation. In. Chiappa KH, ed. *Evoked Potentials in Clinical Medicine.* New York: Raven Press, 1985.
26. Chudler EH, Dong WK. The assessment of pain by cerebral evoked potentials. *Pain* 1983; 16: 221–244.
27. Clark DL, Rosner BS. Anesthesiology. *Anesthesiology* 1973; 38: 564–582.
28. Courtin RF, Bickford RG, Falconer AJR. The classification and significance of electro-encephalographic patterns produced by nitrous oxide–ether anesthesia during surgical operations. *Proceedings of the Staff Meetings of the Mayo Clinic* 1950; 25: 197–206.
29. Crabb I, Thornton C, Konieczko KM, Chan A, Aquilina R, Frazer N, Dore CJ, Newton DEF. Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anaesthesia in a dose dependent manner. *British Journal of Anaesthesia* 1996; 76: 795–801.
30. Davies FW, Mantzardis H, Kenny GNC, Fisher AC. Middle latency auditory evoked potentials during repeated transitions from consciousness to unconsciousness. *Anaesthesia* 1996; 51: 107–113.
31. Derendorf H, Drehsen G, Rohdewald P. Cortical-evoked potentials and saliva levels as basis for the comparison of pure analgesics to analgesic combinations. *Pharmacology* 1982; 25: 227–236.
32. Doi M, Garaj RJ, Mantzaris H, Kenny GNC. Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. *British Journal of Anaesthesia* 1997; 78: 180–184.
33. Erwin R, Buchwald JS. Midlatency auditory evoked responses: differential effects of sleep in the human. *Electroencephalography and Clinical Neurophysiology* 1986; 65: 383–392.
34. Galambos R, Hecox K. Clinical applications of the brainstem auditory potentials. *Progress in Clinical Neurophysiology* 1977; 2: 1–19.
35. Gibbs GA, Gibbs EL, Lennox WG. Effect on the electro-encephalogram of certain drugs which influence nervous activity. *Archives of Internal Medicine* 1937; 60: 154–166.
36. Giblin DR. Somatosensory evoked potentials in healthy subjects and in patients with lesions of the nervous system. *Annals of the New York Academy of Sciences* 1964; 112: 93–142.
37. Gibson SJ, Gorman MM, Helme RD. Assessment of pain in the elderly using event-related cerebral potentials. In: Bond MR, Charlton JE, Woolf CJ, eds *Proceedings of the VIth World Congress on Pain.* Amsterdam: Elsevier, 1991; 527–533.
38. Goldie WD, Chiappa KH, Young RR, Brooks EB. Brainstem auditory and short latency somatosensory evoked responses in brain death. *Neurology* 1981; 31: 248–256
39. Goldman L. Information-processing under general anaesthesia: a review. *Journal of the Royal Society of Medicine* 1988; 81: 224–227.
40. Goldman L, Shah MV, Hebden MW. Memory of cardiac anaesthesia. *Anaesthesia* 1987; 42: 596–603.
41. Halliday AM, McDonald WI, Mushin J. Delayed visual evoked response in optic neuritis. *Lancet* 1972; i: 982–985.
42. Halliday AM, McDonald WI, Mushin J. Visual evoked responses in the diagnosis of multiple sclerosis. *British Medical Journal* 1973; 4: 661–664.

43. Harkins SW, Price DD. Effects of compression block on cerebral evoked potentials in relation to first and second pain. *Pain* 1981; (Suppl 1): 229.
44. Hett DA, Smith DC, Pilkington SN, Abbott TR. Effect of temperature and cardiopulmonary bypass on the auditory evoked response. *British Journal of Anaesthesia* 1995; **75**: 293–296.
45. Hume AL, Cant BR. Conduction time in central somatosensory pathways in man. *Electroencephalography and Clinical Neurophysiology* 1978; **45**: 361–375.
46. Jewett DL. Volume-conducted potentials in response to auditory stimuli as detected by averaging in the cat. *Proceedings of the San Diego Biomedical Symposium* 1970; **28**: 609–618.
47. Jewett DL, Williston JS. Auditory-evoked far fields averaged from the scalp of humans. *Brain* 1971; **94**: 681–696.
48. Jones JG, Konieczko K. Hearing and memory in anaesthetized patients. *British Medical Journal* 1986; **292**: 1291–1293.
49. Jordan C, Weller C, Thornton C, Newton DEF. Monitoring evoked potentials during surgery to assess the level of anaesthesia. *Journal of Medical Engineering and Technology* 1997; **19**: 77–79.
50. Kaga K, Hink RF, Shinoda Y, Suzuki J. Evidence for a primary cortical origin of a middle latency auditory evoked potential in cats. *Electroencephalography and Clinical Neurophysiology* 1980; **50**: 254–266
51. Kavanagh KT, Harker LA, Tyler RS. Auditory brainstem and middle latency responses. *Annals of Otology, Rhinology and Laryngology* 1984; **108**: 1–12.
52. Kochs E, Kalkman CJ, Thornton C, Bischoff P, Kuppe E, Abke J, Stockmans G. Classification of inadequacy of anaesthesia by spontaneous and evoked EEG using neural net and wavelet transformation *Anesthesiology* 1996; **88**: A471.
53. Lam AM, Sharar SR, Mayberg TS, Eng CC Isoflurane compared with nitrous oxide anaesthesia for intraoperative monitoring of somatosensory evoked potentials. *Canadian Journal of Anaesthesia* 1994; **41**: 295–300.
54. Loughnan BL, Sebel PS, Thomas D, Rutherford CF, Rogers H. Evoked potentials following diazepam or fentanyl. *Anaesthesia* 1987; **42**: 195–198
55. Lovrich D, Novick B, Vaughan HG. Topographic analysis of auditory event-related potentials associated with acoustic and semantic processing. *Electroencephalography and Clinical Neurophysiology* 1988; **71**: 40–54.
56. Mauguiere F, Courjon J, Schott B. Dissociation of early SEP components in unilateral traumatic section of the lower medulla. *Annals of Neurology* 1983; **13**: 309–313.
57. Maurer K, Leitner H, Schafer E. Detection and localization of brainstem lesions with auditory evoked potentials. In: Barber C, ed. *Evoked Potentials*. Lancaster: MTP Press, 1980; 391–398.
58. Mor J, Carmon A. Laser emitted radiation for pain research. *Pain* 1975; **1**: 233–237.
59. Mummaneni N, Rao TLK, Montoya A. Awareness and recall with high-dose fentanyl–oxygen anesthesia. *Anesthesia and Analgesia* 1980; **59**: 948.
60. Munglani R, Andrade J, Sapsford DJ, Baddeley A, Jones JG. A measure of consciousness and memory during isoflurane administration: the coherent frequency. *British Journal of Anaesthesia* 1993; **71**: 633–641.
61. Nel MR, Fernandes R, Thornton C, Newton DEF. The auditory evoked response after co-induction of anaesthesia with midazolam and propofol. *British Journal of Anaesthesia* 1998; (in press).
62. Newton DEF, Thornton C, Konieczko KM, Jordan C, Webster NR, Luff NP, Frith CD Dore CJ. Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane. *British Journal of Anaesthesia* 1992; **69**: 122–129.
63. O'Kelly SW, Smith DC, Pilkington SN. The auditory evoked potential and paediatric anaesthesia. *British Journal Anaesthesia* 1995; **75**: 428–430.
64. Petersen-Felix S, Arendt-Nielsen L, Bak P, Fischer M, Zbinden AM. Psychophysical and electrophysiological responses to experimental pain may be influenced by sedation: Comparison of the effects of a hypnotic (propofol) and an analgesic (alfentanil). *British Journal of Anaesthesia* 1996; **77**: 165–171.
65. Picton TW, Hillyard SA. Human auditory evoked potentials II: Effects of attention. *Electroencephalography and Clinical Neurophysiology* 1974; **36**: 191–199.
66. Robinson K, Rudge P. Abnormalities of the auditory evoked potentials in patients with multiple sclerosis. *Brain* 1977; **100**. 19–40.
67. Rossini PM, Kaula RW, House WJ, Cracco RQ. Alteration of brainstem auditory evoked responses following cardio-respiratory arrest and resuscitation. *Electroencephalography and Clinical Neurophysiology* 1982; **54**: 232–234.
68. Roy R, Huang JW. Closed loop intravenous anesthetic administration. *Anesthesiology* 1997; **87**: A641.
69. Savoia G, Esposito C, Belfiore F, Amantea B, Cuocolo R. Propofol infusion and auditory evoked potentials. *Anaesthesia* 1988; **43**: 46–49
70. Schwender D, Daunderer M, Schnatmann N, Klasing S, Finsterer S, Peter K. Midlatency auditory evoked potentials and motor signs of wakefulness during anaesthesia with midazolam. *British Journal of Anaesthesia* 1997, **79**: 53–58.
71. Schwender D, Kaiser A, Klasing S, Peter K, Poppel E. Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. *Anesthesiology* 1994; **80**: 493–501.
72. Schwender D, Keller I, Klasing S, Madler C. Akustisch evozierte Potentiale mittlerer Latenz (AEPML) unter hochdosierter Opioidanalgesie. *Anaesthetist* 1990; **39**· 299–305.
73. Schwender D, Klasing S, Madler C, Poppel E, Peter K. Effects of benzodiazepines on mid-latency auditory evoked potentials. *Canadian Journal of Anaesthesia* 1993; **40**: 1148–1154.
74. Schwender D, Madler C, Klasing S, Poppel E, Peter K. Mid-latency evoked potentials and wakefulness during caesarean section. *European Journal of Anaesthesiology* 1995; **12**: 171–179.
75. Sloan TB, Fugina ML, Toleikis JR. Effects of midazolam on median nerve somatosensory evoked potentials. *British Journal of Anaesthesia* 1990; **64**: 590–593.
76. Sneyd JR, Wang DY, Edwards D, Pomfrett CJ, Doran BR, Healy TE, Pollard BJ. Effect of physiotherapy on the auditory evoked response of paralysed patients in the intensive care unit. *British Journal of Anaesthesia* 1992; **68**: 349–351.
77. Starr A, Achor JL. Auditory brainstem responses in neurological disease *Archives of Neurology* 1975; **32**: 761–768.
78. Stockmanns G, Nahm W, Thornton C, Shannon C, Konecny E, Kochs E. Wavelet-analysis of middle latency auditory evoked potentials during repetitive propofol sedation. *Anesthesiology* 1997; **87**: A465
79. Svensson P, Arendt-Nielsen L, Bjerring P, Kaaber S. Oral mucosal analgesia quantitatively assessed by argon laser-induced thresholds and single evoked vertex potentials. *Anesthesia and Pain Control in Dentistry* 1993; **2**: 154–161.
80. Teas DC, Kiang N. Evoked responses from the auditory cortex. *Experimental Neurology* 1964, **10**: 119.
81. Thompson CRS, Harding GFA. The visual evoked response in patients with cataracts. In: *Documenta Ophthalmologica*. Junk: The Hague, 1978; 193–201.
82. Thornton C. Evoked potentials in anaesthesia. *European Journal of Anaesthesiology* 1992; **8**: 89–107.
83. Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Dore C, Newton DEF. The auditory evoked response as an indicator of awareness. *British Journal of Anaesthesia* 1989, **63**· 113–115.
84. Thornton C, Creagh-Barry P, Jordan C, Luff NP, Dore C, Henley M, Newton DEF Somatosensory and auditory evoked responses recorded simultaneously. differential effects of nitrous oxide and isoflurane. *British Journal of Anaesthesia* 1992; **68**: 508–514.
85. Thornton C, Konieczko K, Jones JG, Jordan C, Dore CJ, Heneghan CPH. Effect of surgical stimulation on the auditory evoked response. *British Journal of Anaesthesia* 1988; **60**: 372–378.
86. Thornton C, Konieczko KM, Knight AB, Kaul B, Jones JG, Dore C, White DC. The effect of propofol on the auditory evoked response and on oesophageal contractility. *British Journal of Anaesthesia* 1989; **63**: 411–417.
87. Thornton C, Newton DEF. The auditory evoked response: a measure of depth of anaesthesia. *Baillieres Clinical Anaesthesiology* 1989; **3**: 559–585.
88. Tooley MA, Greenslade GL, Prys-Roberts C. Concentration-related effects of propofol on the auditory evoked response. *British Journal of Anaesthesia* 1996; **77**: 720–726.
89. Umo-Etuk J, Sharpe RM, Brunner MD, Thornton C. The effect of a bolus dose of midazolam on the auditory evoked response in man. *British Journal of Anaesthesia* 1997; **78**: 464–465P.
90. Woods DL, Clayworth CC, Knight RT, Simpson GV, Naeser MA. Generators of middle and long latency auditory evoked potentials: implications from studies of patients with bitemporal lesions. *Electroencephalography and Clinical Neurophysiology* 1987; **68**: 132–148.

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SHORT COMMUNICATIONS

A single dose of milrinone facilitates separation from cardiopulmonary bypass in patients with pre-existing left ventricular dysfunction[†]

E. B. Lobato, O. Florete jr and H. L. Bingham

Summary

Milrinone is used during cardiac surgery to facilitate separation from cardiopulmonary bypass (CPB) and/or to treat myocardial dysfunction in the post-bypass period. We have demonstrated, in patients with preoperative depression of systolic function undergoing aorto-coronary artery bypass surgery, sustained improvement in cardiac function after a single loading dose of milrinone 50 μg kg^{-1}, administered at the end of bypass, thus significantly decreasing the need for beta-agonist therapy. (*Br. J. Anaesth.* 1998; **81**: 782–784).

Keywords: heart, milrinone; heart, cardiopulmonary bypass; heart, myocardial function; pharmacology, milrinone

Milrinone is an inodilator commonly used to improve myocardial function. Its main mechanism of action is via inhibition of fraction III of the enzyme phosphodiesterase, thus increasing intracellular concentrations of cyclic AMP in the myocardium. The current recommended dose is a bolus of 50 μg kg^{-1}, followed by continuous infusion of 0.5 μg kg^{-1} min^{-1} to maintain therapeutic serum concentrations.[1] The purpose of this study was to test the hypothesis that in patients undergoing coronary artery bypass graft (CABG) surgery with pre-existing mild to moderate systolic dysfunction, prophylactic administration of a single dose of milrinone produces sustained improvement in cardiac function, thus decreasing the need for continuous infusion of milrinone and/or a beta agonist.

Methods and results

After obtaining approval from the local Institutional Review Board, we studied 21 consenting adult patients undergoing coronary revascularization, allocated randomly to receive a single dose of milrinone 50 μg kg^{-1} or placebo (normal saline solution) before separation from CPB. All patients had mild to moderate preoperative left ventricular dysfunction (LVEF) (30–50%).

The anaesthetic technique comprised a total dose of fentanyl 50 μg kg^{-1} and midazolam 0.15 mg kg^{-1}, supplemented with pancuronium and isoflurane. Radial arterial and pulmonary artery catheters (Abbott Laboratories, Mountainview, CA, USA) were inserted after induction of anaesthesia, as is usual in our institution. All pressures were measured with transducers referenced at the level of the right atrium. Cardiac index was determined via thermodilution. A transoesophageal multiplane ultrasound transducer (Omniplane Hewlett-Packard, SONOS 1500, Andover, MA, USA) was placed at the level of the left ventricular short axis at the mid-papillary muscle level. End-diastolic (EDA) and end-systolic (ESA) area were measured, and fractional area of change (FAC) evaluated using automatic border detection. Haemodynamic-derived indices were calculated according to standard formulae.

All patients were operated on by the same surgeon using the same technique. The distal coronary anastomoses were constructed under CPB with moderate hypothermia (bladder temperature 28°C) after application of the aortic cross-clamp. Tepid blood cardioplegia (dilution: 1 part blood, 3 parts crystalloid) was infused via the aortic root and coronary sinus with repeated doses given via the aortic root every 20–30 min. The proximal anastomoses were constructed with a partial occlusion clamp during rewarming, with the heart beating spontaneously or electrically paced.

Towards the end of CPB, patients received a loading dose of milrinone 50 μg kg^{-1} (n=11) or normal saline solution (n=10) over 10 min into the bypass pump. Haemodynamic measurements and FAC were determined within 5 min after termination of CPB, 30 min later and at the end of surgery. Dobutamine, at a starting dose of 5 μg kg^{-1}, was infused if cardiac index was <2.2 litre min^{-1} m^{-2} and pulmonary artery occlusion pressure >12 mm Hg, or if poor contractility of the left ventricle was seen on transoesophageal echocardiography. The dose was increased at the discretion of the anaesthetist until the desired haemodynamic effects were obtained or a maximum dose of 10 μg kg^{-1} min^{-1} was achieved. Further inotropes were administered as required. Phenylephrine 40–80 μg i.v. was administered as required to maintain mean arterial pressure >60 mm Hg as a result of a low SVR.

Physical characteristics and comparison between bypass time and number of grafts were analysed with paired Student's t test and Mann–Whitney tests. Measures were used to generate the haemodynamic and echocardiographic data between groups using one-way repeated measures ANOVA. Requirements

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for dobutamine and phenylephrine were analysed by chi-square test.

There were no significant differences between groups for incidence of congestive heart failure, medication or LVEF before operation. Intraoperative mean CPB time, aortic cross-clamp time, number of grafts, packed cell volume and ionized calcium were also similar. All patients achieved successful separation from CPB during the initial attempt. Dobutamine (mean dose 7 μg kg^{-1} min^{-1}) was required in eight patients in the placebo group compared with none in the milrinone group immediately after termination of CPB ($P<0.05$). At 30 min after CPB, three patients in the milrinone group required dobutamine (mean dose 5 μg kg^{-1} min^{-1}). No further inotropic adjustment was necessary in any of these patients at the end of surgery. Haemodynamic data from both groups after CPB are shown in table 1. There was no difference in heart rate between groups; cardiac index and FAC were significantly higher, and SVRI was consistently lower in the milrinone group at all times. With milrinone, 5 of 11 patients required phenylephrine to maintain mean arterial pressure >60 mm Hg compared with two of 10 patients in the placebo–dobutamine group ($P<0.05$). Time from termination of CPB to the end of surgery averaged 70 min in the milrinone group and 72 min in the placebo group.

Comment

Milrinone has been used for the treatment of low output syndrome caused by myocardial dysfunction after CPB. It is more potent than amrinone, and its use is not associated with thrombocytopenia. Pharmacokinetic data have shown that, unlike amrinone, when milrinone is administered before termination of bypass, no modifications in the loading dose for the added volume of the CPB circuit are necessary.[1] Milrinone 50 μg kg^{-1}, given 10–20 min before the end of extracorporeal circulation, produces concentrations greater than 100 ng dl^{-1} which are associated with an increased cardiac index.[1] However, after a loading dose, serum concentrations decline within 30 min; thus, in the presence of normal renal function, continuous infusion of 0.5 μg kg^{-1} min^{-1} is recommended to maintain serum concentrations greater than 100 ng dl^{-1}.[1] Our results confirm the experience of Butterworth and colleagues who demonstrated improved haemodynamic state and lesser need for inotropes in patients receiving amrinone compared with placebo at the end of CPB.[2] We observed that administration of a single prophylactic loading dose of milrinone was associated with significant improvement in haemodynamic state in addition to echocardiographic indices of systolic function, comparing favourably with those receiving dobutamine in the placebo group. Haemodynamic improvement was still present 70 min after bypass. Phenylephrine was required more often in milrinone-treated patients (but without adverse effect). In our experience and that of others, phenylephrine is commonly used to treat excessive vasodilatation and is not associated with adverse effects.

Milrinone improves cardiac function by increasing contractility and decreasing afterload.[3] It also improves coronary blood flow and may improve recovery after myocardial stunning.[4] It is possible that while serum concentrations seem to correlate with the inotropic effects of the drug, effects on the systemic vasculature and myocardial blood flow after reperfusion may contribute to the more pronounced and sustained improvement seen in this group of patients, even after serum concentrations based on previous pharmacokinetic data might have declined to subtherapeutic levels. Separate analysis of the inotropic from the vasodilatory effects of inodilators is possible via determination of end-systolic and arterial elastance using pressure–volume loops;[5] however, this was not the objective of the study. Also, as suggested with amrinone, administration of milrinone may offer some protection from post-bypass ischaemia, which would result in long term improved performance.[6]

In summary, we have shown that in patients with mild depression of systolic function before operation, administration of a loading dose of milrinone 50 μg kg^{-1} was associated with sustained haemodynamic improvement, in addition to increases in cardiac function that persisted until the end of surgery.

Table 1 Haemodynamic data in the milrinone and placebo groups (mean (SEM)). CPB=Cardiopulmonary bypass; HR=heart rate; MAP=mean arterial pressure; MPAP=mean pulmonary artery pressure; PAOP=pulmonary artery occlusion pressure; CVP=central venous pressure; CI=cardiac index; SVI=stroke volume index; SVRI=systemic vascular resistance index; PVRI=pulmonary vascular resistance index; LVSWI=left ventricular stroke work index; RVSWI=right ventricular stroke work index; FAC=fraction of area of change. $P<0.05$ compared with placebo· *at the end of CPB; †30 min after CPB; and ‡end of surgery

	Milrinone			Placebo		
	Post-CPB	CPB+30 min	End of Surgery	Post CPB	CPB+30 min	End of Surgery
HR (beat min^{-1})	96 (17)	100 (10)	102 (11)	102 (81)	10 (9)	99 (7)
MAP (mm Hg)	68 (4)*	70 (8)	76 (4)	77 (4)	75 (8)	76 (6)
MPAP (mm Hg)	22 (6)	24 (6)	23 (4)	24 (3)	23 (3)	23 (3)
PAOP (mm Hg)	12 (2)*	13 (3)	14 (2)	17 (2)	16 (2)	16 (2)
CVP (mm Hg)	14 (4)	12 (2)	13 (2)	13 (5)	14 (3)	12 (1)
CI (litre min^{-1} m^{-2})	3.4 (0.2)*	2.9 (0.3)†	3.3 (0.2)‡	2.2 (0.3)	2.2 (0.1)	2.3 (0.1)
SVI (mL beat^{-1} m^{-2})	31 (4)*	29 (2)	33 (4)‡	22 (3)	24 (3)	25 (2)
SVRI(dynes sec^{-1} m^{-2} cm^{-5})	1398 (139)*	1754 (175)†	1509 (153)‡	2293 (116)	2310 (108)	2280 (60)
PVRI(dynes sec^{-1} m^{-2} cm^{-5})	216 (25)*	232 (23)	217 (8)‡	263 (50)	248 (32)	251 (35)
LVSWI(gm m^{-1} beat^{-1} m^{-2})	29 (9)*	24 (7)	30 (4)‡	19 (2)	21 (2)	21 (2)
RVSWI(gm m^{-1} beat^{-1} m^{-2})	9 (4)*	7 (4)	9 (4)‡	4 (1)	5 (1)	5 (1)
FAC (%)	45 (5)*	40 (6)†	43 (3)‡	32 (1)	34 (1)	32 (1)

References

1. Bailey JM, Levy JH, Kijusa M, Szlam F, Hug CC. Pharmacokinetics of milrinone during cardiac surgery. *Anesthesiology* 1994; **81**: 945–951.
2. Butterworth JF IV, Royster RL, Prielipp RC, Lawless ST, Wallenhaupt SL. Amrinone in cardiac surgical patients with left ventricular dysfunction. A prospective randomized placebo-controlled trial. *Chest* 1993; **104**: 1660–1667.
3. Feneck RO, and the European Milrinone Multicenter Trial Group. Intravenous milrinone following cardiac surgery: II. Influence of baseline hemodynamics and patient factors on therapeutic response. *Journal of Cardiothoracic and Vascular Anesthesia* 1992; **6**: 563–567.
4. Grose R, Strain J, Greenberg M, LeJemtel TH. Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure. *Journal of the American College of Cardiology* 1986; **7**: 1107–1113.
5. Gorcsan J, Gasior TA, Mandarino WA, Deneault LG, Hattler BG, Pinsky MR. Assessment of the immediate effects of cardiopulmonary bypass on left ventricular performance by on-line pressure area relations. *Circulation* 1994; **89**: 180–190.
6. Ko W, Zelano JA, Fahey AL, Berman K, Lang D, Ison OW, Krieger KH. The effects of amrinone versus dobutamine on myocardial mechanics and energetics after hypothermic global ischemia. *Journal of Thoracic and Cardiovascular Surgery* 1993; **105**: 1015–1024.

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Effect of remifentanil on the auditory evoked response and haemodynamic changes after intubation and surgical incision

R. R. McGregor, L. G. Allan, R. M. Sharpe, C. Thornton and D. E. F. Newton

Summary

We have observed the effect of intubation and incision, as measured by the auditory evoked response (AER) and haemodynamic variables, in 12 patients undergoing hernia repair or varicose vein surgery who received remifentanil as part of either an inhaled anaesthetic technique using isoflurane or as part of a total i.v. technique using propofol. Anaesthesia was induced with remifentanil 1 μg kg^{-1} and propofol, neuromuscular block was achieved with atracurium 0.6 mg kg^{-1} before intubation, and anaesthesia was maintained with a continuous infusion of remifentanil in combination with either a continuous infusion of propofol or inhaled isoflurane. The AER and haemodynamic variables were measured before and after intubation and incision. The effects of intubation and incision on the AER and haemodynamic variables were not significantly different between the remifentanil–propofol and remifentanil–isoflurane groups. However, the study had a low power for this comparison. When the data for the two anaesthetic combinations were pooled, the only significant effects were increases in diastolic arterial pressure and heart rate immediately after intubation; these were not seen 5 min after intubation. There were no cardiovascular responses to incision. There were no significant changes in the AER after intubation or incision. (*Br. J. Anaesth.* 1998; **81**: 785–786).

Keywords: analgesics opioid, remifentanil; anaesthesia, depth; brain, evoked potentials; cardiovascular system, effects; intubation tracheal

In this study, we have observed two different anaesthetic techniques, each in combination with remifentanil. We assessed cortical and autonomic arousal by examining the auditory evoked response (AER) and haemodynamic changes in response to intubation and incision. The AER has been shown to be a useful monitor of depth of anaesthesia[1]; the amplitude of the early cortical waves of the AER has been shown to be a sensitive measure of anaesthetic concentration and to respond to laryngoscopy[2] and surgical stimulation.[3] Therefore, the AER reflects the balance between CNS depression caused by anaesthetic drugs and arousal caused by surgical or other stimuli.

Methods and results

After obtaining approval from Harrow Research Ethics Committee and written informed consent, we studied 12 ASA I–II patients undergoing elective hernia repair or varicose vein surgery. They were allocated randomly to receive maintenance anaesthesia with either remifentanil–isoflurane or remifentanil–propofol. None received premedication. All patients were given Hartmann's solution 5 ml kg^{-1}, glycopyrrolate 0.2 mg i.v., and the lungs were preoxygenated with 100% oxygen for 3 min. A loading bolus dose of remifentanil 1 μg kg^{-1} was administered over 30–60 s, followed by infusion of remifentanil 0.5 μg kg^{-1} min^{-1}. Propofol (mean 80 mg) was then administered by slow injection, 10 mg every 10 s, until loss of consciousness. After achieving neuromuscular block with atracurium 0.6 mg kg^{-1}, the trachea was intubated. Those receiving inhaled isoflurane for maintenance of anaesthesia were administered 0.6% end-tidal isoflurane in an air–oxygen mixture. Those receiving propofol were given a continuous infusion of propofol 9 mg kg^{-1} h^{-1}, reducing to 6 mg kg^{-1} h^{-1} after 10 min. The infusion of remifentanil was decreased to 0.25 μg kg^{-1} min^{-1}, 5 min after intubation, and rectal diclofenac (100 mg) was administered. Intraoperative surgical stress responses (e.g. hypertension or tachycardia) were controlled by adjustments of the propofol infusion or end-tidal isoflurane concentration and/or remifentanil infusion, as was hypotension. Persistent hypotension or bradycardia was treated with ephedrine or glycopyrrolate.

Details of the AER recording have been described previously.[4] The EEG was recorded from adhesive silver–silver chloride electrodes attached at the mastoid and forehead. A rarefaction click stimulus was delivered at 6 s^{-1} to each ear simultaneously through close-fitting ear pieces at 75 dB above the average hearing threshold. Average AER waveforms corresponding to 2 min 40 s (1024 sweeps) before and after intubation and skin incision were derived. Pa and Nb amplitudes and latencies were measured from these waveforms. Haemodynamic measurements were obtained 1 min before and 1 and 5 min after intubation and incision. Analysis of variance was used to study differences between variables.

The results from the 12 patients are summarized in table 1. There was no significant difference between the remifentanil–propofol group and the remifentanil–isoflurane groups for the AER or haemodynamic variables. Nb amplitude increased on intubation in the propofol group while it decreased in the isoflurane group (P=0.04). As this change was

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Table 1 AER and haemodynamic variables (mean (95% confidence intervals)) at various times during the study. *P=0.035, †P=0.014, after *vs* before intubation SAP=Systolic arterial pressure; DAP=diastolic arterial pressure; HR=heart rate

	Pa amplitude (μV)	Pa latency (ms)	Nb amplitude (μV)	Nb latency (ms)	SAP (mm Hg)	DAP (mm Hg)	HR (beat min^{-1})
1 min before intubation	0.43 (0.34–0 53)	36.2 (34.4–38.0)	0.31 (0.26–0.38)	56.5 (53.5–59.8)	91 (82–100)	49 (43–55)	61 (56–65)
1 min after intubation	0.39 (0.32–0.49)	36.0 (34.2–37.8)	0.32 (0.26–0.38)	55.2 (52.2–58.4)	103 (93–112)	58 (52–64)*	69 (64–73)†
1 min before incision	0.32 (0.26–0.40)	37.7 (35.9–39.6)	0.25 (0.21–0.31)	55.9 (52.9–59.0)	98 (88–107)	56 (50–62)	60 (55–65)
1 min after incision	0.29 (0.24–0.36)	37.5 (35.7–39.4)	0.27 (0.22–0.33)	56 6 (53.5–59.8)	96 (87–105)	58 (55–65)	62 (57–67)

not supported, as would be expected, by other related AER variables, we dismissed it as a chance finding. There was no significant difference in the use of rescue medication between groups. The data were pooled and we found that there was no overall response to laryngoscopy, intubation or incision, as measured by the AER. On intubation, the only significant changes were increases in diastolic arterial pressure and heart rate. There were no haemodynamic changes associated with incision.

Comment

After induction of anaesthesia with remifentanil 1 μg kg^{-1} and propofol (mean 80 mg), intubation produced no significant change in the AER. In this study we were dependent on historical controls because it was not considered ethical to substitute either a placebo or nitrous oxide for remifentanil. Previous studies by our group have demonstrated increases in Pa amplitude of 53%, 36% and 60% in response to succinylcholine,[5] laryngoscopy[2] and intubation (Shinner G, Sharpe RM, Shannon C, Thornton C, Doré CJ, Brunner MD. Bolus doses of alfentanil prevent the rise in Pa amplitude associated with intubation in a dose-dependent fashion, personal communication). This study would have been sensitive enough to detect an increase in Pa amplitude, with intubation or incision, of 29% at the 5% significance level with a power of 80%.

AER arousal is often accompanied by an autonomic response which may prove detrimental to patients with cardiovascular disease. Maintenance of anaesthesia with either propofol or isoflurane in combination with infusion of remifentanil also resulted in abolition of the AER response to surgical incision. The cardiovascular response to intubation and incision was limited to an increase in diastolic arterial pressure and heart rate which was no longer present 5 min after intubation. Other studies have reported attenuation or abolition of the cardiovascular response with this dose of remifentanil. In our study, we found heart rate and diastolic arterial pressure responses to intubation. The fact that no AER response was seen could indicate that the AER is a less sensitive measure of depth of anaesthesia compared with cardiovascular changes. However, it is more likely that these variables measure different aspects of depth of anaesthesia.

It is very difficult to determine equipotent concentrations of inhalation or i.v. anaesthetics, such as isoflurane and propofol, and in particular in combination with remifentanil. However, there was no significant difference between changes in any of the variables measured in the isoflurane group compared with the propofol group, with the concentrations used in this study. The study had low power for comparing the remifentanil–isoflurane and remifentanil–propofol regimens because of the small number of subjects in each group (n=6).

In summary, we conclude that remifentanil (bolus dose of 1 μg kg^{-1} followed by infusion) in combination with either propofol 6 mg kg^{-1} h^{-1} or 0.6% end-tidal isoflurane obtunded the early cortical effects of intubation and incision.

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References

1. Thornton C. Evoked potentials in anaesthesia. *European Journal of Anaesthesiology* 1991; 8: 89–107.
2. Richmond CE, Matson A, Thornton C, Doré CJ, Newton DEF. Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response. *British Journal of Anaesthesia* 1996; 76· 446–448.
3. Thornton C, Konieczko K, Jones JG, Jordan C, Doré CJ, Heneghan CPH. Effect of surgical stimulation on the auditory evoked response. *British Journal of Anaesthesia* 1988; 60: 372–378.
4. Jordan C, Weller C, Thornton C, Newton DEF. Monitoring evoked potentials during surgery to assess the level of anaesthesia *Journal of Medical Engineering and Technology* 1995; 19· 77–79.
5. Brunner MD, Nathwani D, Rich PA, Thornton C, Doré CJ, Newton DEF. Effect of suxamethonium on the auditory evoked response in humans. *British Journal of Anaesthesia* 1996; 76: 34–37.

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Vital capacity and tidal volume preoxygenation with a mouthpiece

S. Winship and A. Skinner

Summary

We have measured oxygen wash-in in 20 volunteers undergoing preoxygenation with a face mask, mouthpiece alone and a mouthpiece with a noseclip, in a crossover study. Tidal volume breathing and maximal deep breath techniques were studied with each type of equipment. When tidal volume breathing was used, the face mask and mouthpiece with noseclip were comparable, but the mouthpiece alone achieved a lower end-expiratory oxygen concentration than the two other methods after 3 min ($P<0.001$ and $P<0.01$), and after 5 min ($P<0.05$ in each case). Conversely, during preoxygenation with vital capacity breaths, the mouthpiece and mouthpiece with noseclip were comparable, and both were more effective than the face mask ($P<0.001$). In a second study, 20 patients who had undergone preoxygenation before induction of anaesthesia were asked later if they would have preferred the face mask or mouthpiece for this procedure. Significantly more patients (14 of 18 who expressed a preference) favoured the mouthpiece ($P<0.05$; confidence limits 0.56–0.92). (*Br. J. Anaesth.* 1998; **81**: 787–789).

Keywords. anaesthetic techniques, preoxygenation; equipment, face mask; equipment, mouthpiece; measurement techniques, oxygraphy

Arterial desaturation is common during induction of anaesthesia and can be prevented by preoxygenation.[1] However, preoxygenation with a face mask is inefficient unless it is applied firmly.[2] Some patients are afraid of firm application of the mask, in some the mask fits poorly because of the shape of the face or dentition, and in others a mask cannot be applied because of facial burns or trauma. Thus it is important to offer an alternative.

In this study, first, we investigated in volunteers the effectiveness of a nebulizer-type mouthpiece, with and without a noseclip, compared with a face mask, for vital capacity and tidal volume preoxygenation. Second, we asked if patients preferred a mouthpiece.

Methods and results

After obtaining approval from the Ethics Committee, we studied 20 healthy volunteers allocated sequentially to receive 100% oxygen from each of three types of breathing apparatus: face mask (East Healthcare), mouthpiece (Intersurgical) or a mouthpiece with a noseclip (Speedo) occluding the nares. The noseclip was also used with the face mask. Tidal volume breathing was used for 5 min, and vital capacity breathing for a total of 5 breaths. Oxygen 10 litre min^{-1} was given to each subject from a standard anaesthetic machine via a Mapleson A breathing system with a 4-litre reservoir bag.

Using a Capnomac Ultima gas analyser (Datex Instrumentarium Corporation), calibrated between each set of measurements, inspiratory and expiratory oxygen and carbon dioxide concentrations were measured from each subject's oral cavity via a catheter which was held within a bite-block when the face mask was used, and within the mouthpiece when it was used, both lying 2.5 cm within the subject's mouth. Adequacy of oxygen supply was confirmed by achievement of an inspiratory oxygen concentration of 100%, and adequacy of ventilation by a normal capnogram trace. Between each recording from the same subject, the lungs were allowed to equilibrate with room air.

During tidal volume breathing, end-expiratory oxygen concentration ($F\text{E}'_{O_2}$) was recorded every 20 s during the 5 min of preoxygenation, enabling a wash-in curve to be drawn. During vital capacity breathing, $F\text{E}'_{O_2}$ was recorded at the end of each breath.

As this was a cross-over study, each subject undergoing preoxygenation using all six techniques, they acted as their own controls. A Kruskal–Wallis test was used to analyse $F\text{E}'_{O_2}$ results between all three groups at 180 and 300 s of tidal volume breathing. The mouthpiece and mouthpiece with noseclip results were then independently compared with the face mask results using a Mann–Whitney *U* test. Data from the fourth and fifth vital capacity breaths were analysed in the same way.

At 180 and at 300 s, $F\text{E}'_{O_2}$ was similar using the face mask or mouthpiece with noseclip when tidal volume breathing was used. However, the results of the mouthpiece alone were significantly less ($P<0.001$ in both cases at 180 s; at 300 s, $P<0.01$ compared with the face mask and $P<0.05$ compared with the mouthpiece and noseclip) (fig. 1). Thirteen of the subjects (designated subgroup A) achieved an $F\text{E}'_{O_2}$ concentration of 90% or above with the mouthpiece alone at some point during the study, while seven subjects (subgroup B) never achieved this concentration. Application of the noseclip improved the results of subgroup B, which were not significantly different from the face mask results of subgroup B.

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Table 1 Mean (range) [SD] end-tidal oxygen concentration (%) at 3 and 5 min of tidal volume breathing, and at the fourth and fifth vital capacity breaths. For "all groups", the mouthpiece and mouthpiece with noseclip were compared with the face mask. For "subgroup B", who never achieved an FE'_{O_2} greater than 90% using the mouthpiece, the mouthpiece and mouthpiece with noseclip were compared with the face mask *$P<0.05$, **$P<0.01$ and ***$P<0.001$

	All groups			Sub-group B		
	Face mask	Mouthpiece	Mouthpiece and noseclip	Face mask	Mouthpiece	Mouthpiece and noseclip
3 min	91.7 (86–94) [2.23]	78.95 (44–95) [16.22]	88.8 (62–96) [8.56]	91.3 (85–95) [3.4]	64.6 (38–89) [16.11]***	83.4 (65–94) [11.03]
5 min	91.4 (85–95) [2.95]	70.3 (38–92) [16.69]*	89.3 (73–94) [6.66]	90.7 (88–94) [1.97]	60.1 (44–81) [12.69]**	87.4 (73–94) [7.18]
Fourth vital capacity breath	75 (56–86) [8.41]	84 (76–92) [4.68]***	83 (72–92) [5.73]***	76 (64–84) [7.16]	84 (77–89) [4.64]*	81 (72–89) [5.59]*
Fifth vital capacity breath	76 (59–87) [8.64]	87 (79–93) [4.26]***	86 (71–92) [5.60]***	76 (61–86) [8.80]	86 (79–91) [3.86]***	83 (71–91) [6.37]*

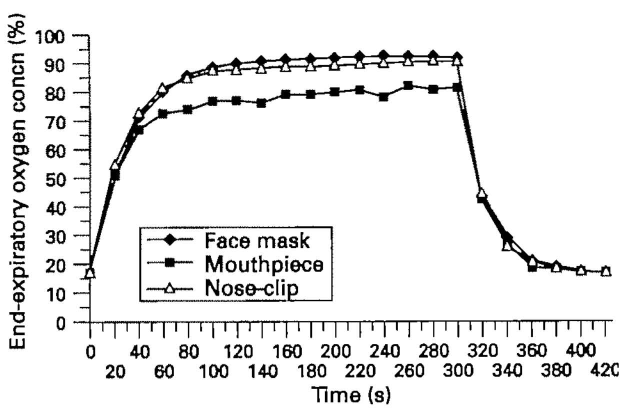

Figure 1 Mean values for end-expiratory oxygen concentration during (0–300 s) and after (320–440 s) administration of 100% oxygen, using the three pieces of equipment for tidal volume preoxygenation.

During preoxygenation with vital capacity breaths, the mouthpiece was significantly better than the face mask, whether or not the noseclip was used ($P<0.001$ at both the fourth and fifth breaths in both instances). Results from subgroup A and subgroup B during vital capacity breathing were similar, and both were significantly higher when using the mouthpiece compared with the face mask ($P<0.01$ and $P<0.05$, respectively, after the fourth vital capacity breath; $P<0.001$ and $P<0.01$, respectively, after the fifth vital capacity breath) (table 1).

In the second part of the study, 20 patients who had undergone preoxygenation before uncomplicated surgery within the preceding few days were shown a Magill breathing system with interchangeable black face mask and mouthpiece, and asked if they had any preference. The results were analysed using the binomial distribution of probabilities. Of the 20 patients (12 females), 14 preferred the mouthpiece, four the face mask and two had no preference. These results were significant ($P<0.05$, confidence levels 0.56–0.92).

Comment

Preoxygenation creates an oxygen reservoir within the patient's lungs. Three and 5 min of tidal volume breathing have variously been recommended. Four maximal deep breaths cause a similar increase in arterial oxygen tension compared with former techniques,[3] but provide less protection from apnoea.[4] Nonetheless, this technique still provided a considerable "apnoea time" in all subjects and was less time-consuming and widely accepted. It is only in cases of anticipated difficult intubation or upper airway obstruction that 3 min of preoxygenation is considered essential. End-tidal oxygen concentration correlates with alveolar partial pressure of oxygen,[5] and is well established as a measure of preoxygenation.

Everatt and Ng recently investigated the mouthpiece for preoxygenation, although they studied its use only during tidal volume breathing.[6] Our results confirm their findings that during tidal volume breathing, the face mask is more reliable than the mouthpiece alone. This is probably because of inadvertent nasal breathing, as application of a noseclip improved FE'_{O_2}. There may also have been leaks around the mouthpiece if the lips were not firmly sealed around it. After the initial increase in FE'_{O_2}, the mean results recorded for the mouthpiece alone fluctuated, probably representing lapses in concentration on the part of some subjects, one-third of whom were unable to achieve an FE'_{O_2} of 90% or more.

Conversely, the mouthpiece was more effective than the face mask for vital capacity preoxygenation. This was probably because of the mechanics of deep breathing. When taking a maximal inspiratory breath it is easier to breathe through the mouth, rather than through the nose, as it presents less resistance. There may be the tendency to purse one's lips at the same time, improving the seal of the lips around the mouthpiece. The poor performance of the face mask during deep breathing is difficult to explain: it may be that the cheeks are sucked in by the negative inspiratory pressure, leading to leaks around the side of the mask. It is reassuring to note that volunteers in subgroup B who, during tidal volume breathing, required the noseclip to be used with the mouthpiece to render it effective, still showed significantly improved FE'_{O_2} values for the mouthpiece compared with the face mask during vital capacity breathing.

In summary, for a vital capacity preoxygenation technique in volunteers, the mouthpiece was more effective than the face mask and, given the greater patient acceptance, it could be considered the technique of choice. If a 3-min period of tidal volume breathing is to be used, the mouthpiece must be used with a noseclip, unless oxygraphy is available to demonstrate adequate oxygen wash-in.

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References

1. Kung MC, Hung CT, Ng KP, Au TK, Lo R, Lam A. Arterial desaturation during induction in healthy adults: should preoxygenation be a routine? *Anaesthesia and Intensive Care* 1991; **19**: 192–196.
2. McGowan P, Skinner A. Preoxygenation—the importance of a good face mask seal. *British Journal of Anaesthesia* 1995; **75**: 777–778.
3. Gold MI, Duarte I, Muravchick S. Arterial oxygenation in conscious patients after 5 minutes and after 30 seconds of oxygen breathing. *Anesthesia and Analgesia* 1981; **60**: 313–315.
4. Gambee AM, Hertzka RE, Fisher DM. Preoxygenation techniques: comparison of the three minutes and four breaths. *Anesthesia and Analgesia* 1987; **66**: 468–470.
5. Myles PS, Heap M, Langley M. Agreement between end-tidal oxygen concentration and the alveolar gas equation: pre- and post-cardiopulmonary bypass. *Anaesthesia and Intensive Care* 1993; **21**: 240.
6. Everatt J, Ng WS. Pre-oxygenation using a face mask or mouthpiece with and without nose clip: patient preferences and efficacy. *Anaesthesia* 1998, **53**: 382–403.

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CASE REPORTS

Anaesthesia for Caesarean section in the presence of severe primary pulmonary hypertension

R. O'Hare, C. Mc Loughlin, K. Milligan, D. McNamee and H. Sidhu

Summary

We describe the case of a pregnant woman, 35 weeks' gestation, with primary pulmonary hypertension and coarctation of the aorta requiring emergency Caesarean section under general anaesthesia. The patient had a pulmonary artery catheter inserted before operation which revealed pulmonary artery pressures in excess of 80/40 mm Hg. These were lowered using an infusion of glyceryl trinitrate. After delivery of the baby and administration of oxytocin, pulmonary artery pressures were more difficult to control. An infusion of prostacyclin was substituted which stabilized pulmonary pressures. After operation, she was transferred to the intensive care unit where prostacyclin was administered by an "aerosolized" route. Her trachea was extubated after 48 h and she made an uneventful recovery. (*Br. J. Anaesth.* 1998; **81**: 790–792).

Keywords: complications, primary pulmonary hypertension; anaesthesia, obstetric

Primary pulmonary hypertension is a rare condition and in association with pregnancy can result in high maternal mortality.[1] The literature on these patients is scant and inconclusive with regard to anaesthetic management.[2,3] We describe our management of such a case, which was made more difficult by an associated coarctation of the aorta and a possible diagnosis of asthma.

Case report

A 25-yr-old multiparous woman presented to the anaesthetic department for an urgent Caesarean section with a diagnosis of severe primary pulmonary hypertension and associated mild coarctation of the aorta. Until the morning of surgery, the patient had not been seen by an anaesthetist. This was her third pregnancy, the previous two being essentially normal deliveries, apart from one episode of dyspnoea and wheezing during her second pregnancy which was treated with salbutamol inhaler. A diagnosis of asthma had been made. No further investigation of her "asthma" was undertaken at that stage. No diagnosis of primary pulmonary hypertension had been made prior to this pregnancy.

During this pregnancy the patient was noted to have a loud pansystolic murmur at the left sternal edge at a 28-week antenatal clinic. She was referred for cardiology consultation and underwent echocardiography which revealed severe pulmonary hypertension and an associated coarctation of the aorta. Pulmonary artery pressures were in excess of 80/40 mm Hg (normal 25/10 mm Hg) and the right ventricle was dilated and hypokinetic. Although initially asymptomatic, she was admitted at 35 weeks' gestation complaining of dyspnoea with a differential diagnosis of heart failure or pneumonia. She was treated with diuretics and after a significant diuresis her clinical condition improved.

However, on the following day, she became tachycardic, tachypnoeic and on auscultation had generalized rhonchi and basal crepitations. This was associated with a decreasing Sa_{O_2}, despite added oxygen. A chest x-ray showed increased interstitial markings. At this stage, cardiotocography tracings showed evidence of fetal distress and it was decided that, in the interest of mother and baby, urgent delivery should be effected. Induction of labour was considered inappropriate and Caesarean section was planned. The patient was admitted to the high dependency unit where an arterial cannula and pulmonary artery flotation (PAF) catheter were inserted and her cardiac indices measured (table 1). Pulmonary artery pressures were extremely labile and fluctuated markedly with minimal stimulation, such as insertion of a peripheral cannula. An infusion of glyceryl trinitrate (GTN) was commenced at a rate of 50 mg h^{-1} via the PAF catheter and this was associated with a reduction in heart rate and pulmonary artery pressures, and some improvement in cardiac output (table 1). An infusion of epoprostenol (prostacyclin) was also prepared for use if required.

We decided to proceed under general anaesthesia and the patient was taken to the operating theatre. After preoxygenation and application of cricoid pressure, anaesthesia was induced with alfentanil 1 mg, etomidate 16 mg and succinylcholine 100 mg. The trachea was intubated and the lungs ventilated with

Table 1 Cardiac indices before and during infusion of glyceryl trinitrate (GTN)

	Before GTN	During GTN
Heart rate (beat min^{-1})	105	86
Systemic AP (mm Hg) (mean)	127/60 (79)	129/70 (89)
Pulmonary AP (mm Hg) (mean)	88/62 (71)	64/43 (50)
SVR (dyn s^{-1} cm^{-5})	1464	1209
PVR (dyn s^{-1} cm^{-5})	600	177
Cardiac output (litre min^{-1})	4.53	5.88
Sa_{O_2} (FI_{O_2}=60%)	92%	Not recorded

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Table 2 Cardiac indices after delivery and during infusion of prostacyclin

	After delivery	With prostacyclin
Heart rate (beat min^{-1})	105	86
Systemic AP (mm Hg) (mean)	98/45 (63)	129/70 (90)
Pulmonary artery AP (mm Hg) (mean)	96/52 (57)	58/32 (41)
SVR (dyn s^{-1} cm^{-5})	1032	1321
PVR (dyn s^{-1} cm^{-5})	432	153
Cardiac output (litre min^{-1})	4.6	5.3

isoflurane and 50% nitrous oxide in oxygen. Neuromuscular block was achieved with vecuronium.

In the peroperative period, the GTN infusion was increased sequentially up to 100 mg h^{-1} to maintain pulmonary artery pressures close to pre-induction values. Initially, this was achieved without a dramatic effect on the systemic circulation. Central venous pressure was maintained at 10–14 mm Hg throughout the operation. After delivery of a healthy 3000-g baby, oxytocin 5 u. were administered slowly over 2 min. It became increasing difficult to maintain control of pulmonary artery pressures without adversely affecting systemic pressures and at one stage these were similar (systemic 98/45 mm Hg *vs* pulmonary 96/52 mm Hg), despite adequate preload. The infusion of GTN was discontinued and an infusion of prostacyclin (epoprostenol) was started using the proximal lumen of the PAF catheter, at a rate of 2 ng kg^{-1} min^{-1}, increasing slowly to 5 ng kg^{-1} min^{-1}. This appeared to give selective control of pulmonary artery pressures while preserving other cardiac indices within acceptable limits (table 2).

Surgery was completed uneventfully. After operation, the patient was admitted to the intensive care unit where artificial ventilation was continued. Shortly afterwards, vaginal bleeding became problematic which was thought to be secondary to infusion of prostacyclin. To avoid systemic effects, the route of administration of prostacyclin was changed: it was nebulized into the inspiratory limb of the ventilator (4 ml of concentrated epoprostenol (20 000 ng ml^{-1}) nebulized at a rate of 3 ml h^{-1}). The infusion of prostacyclin via the pulmonary catheter was gradually reduced and eventually stopped as the effects of the aerosolized drug became established. Pulmonary artery pressures remained low and vaginal bleeding stopped. Nasogastric nifedipine 30 mg was administered and the prostacyclin reduced after 24 h. During the postoperative period, the patient was sedated using an infusion of propofol and received morphine infusion for analgesia. The trachea was extubated after 48 h and she had an uneventful post-partum period.

Discussion

Primary pulmonary hypertension is uncommon. It is a disease of unknown aetiology; the pulmonary vasculature undergoes extensive remodelling, elevating pulmonary artery pressure and pulmonary vascular resistance. Primary pulmonary hypertension can occur at any age and in both sexes, but most commonly affects women in young adulthood or middle age.[4] While the literature on the management of non-pregnant patients with this condition is relatively extensive, information on the pregnant patient is scarce. The literature reports a mortality rate of 50% for vaginal delivery and approaching 100% for Caesarean section.

In patients suffering from pulmonary hypertension, cardiac output from the right ventricle is critically dependent on filling pressure from the venous return and pulmonary pressure. It may be seriously impaired by minor stimuli causing increases in heart rate and pulmonary vascular resistance, or a decrease in venous return. Minor stimuli such as conversation, surgical discomfort or stress, although inconsequential to healthy individuals, may have dramatic effects. The commonest fatal sequence of events described is a minor stimulus causing a tachycardia or an increase in pulmonary vascular resistance followed by collapse that is unresponsive to treatment.

It is unclear if Caesarean section should be performed under epidural block or general anaesthesia. Roberts and Keast[1] in their review of pulmonary hypertension in pregnancy, based on two previous cases and two cases in their own experience, reported that only one patient had survived Caesarean section and this was under general anaesthesia. Regional block may cause a reduction in venous return which impairs output from the right ventricle. Reflex tachycardia may also reduce cardiac contractility during local block. Alternatively, a general anaesthetic may produce serious and unpredictable reductions in pulmonary blood flow, especially in the presence of a failing right ventricle.

Our patient presented to the anaesthetic team as an emergency on the morning of Caesarean section. She described no problems during this pregnancy and it was not until she was in *extremis* that she actually sought medical assistance. This may be part of the explanation as to why the severity of her condition was not realized until this late stage. Earlier presentation would have allowed a joint approach between the obstetric, cardiology and anaesthetic teams and we may have managed the anaesthetic differently. In that situation, we would have encouraged vaginal delivery under regional block, as described by Smedstad, Cramb and Morison.[5] They describe the management of eight cases of pulmonary hypertension, seven of whom had the benefit of a joint approach to management from early in pregnancy; all had vaginal deliveries and survived. The eighth case was a patient who was admitted as an emergency complaining of dyspnoea. This patient underwent general anaesthesia for Caesarean section and later died.

We decided to perform a general anaesthetic as we felt more confident that we could maintain critical filling pressures to the right ventricle and be more likely to control increases in pulmonary vascular resistances associated with intubation or surgical stimulation. Our patient showed evidence that any anxiety had an effect on her pulmonary vasculature. Our decision was only marginally influenced by coarctation of the aorta, which we felt was of minor significance.

The literature suggests that patients with pulmonary hypertension have an unpredictable response to the effects of vasoactive drugs.[6] Our patient was admitted to a high dependency unit before operation and had invasive monitoring while an infusion of GTN was started at a low rate. This effectively reduced pulmonary pressures and pulmonary vascular resistance while increasing cardiac indices. GTN is an effective pulmonary dilator with lesser effects on the systemic vasculature. It has minimal effects on the fetus and uterine activity. These properties make it the agent of first choice. An alternative agent may have been sodium nitroprusside, which would have been an effective pulmonary vasodilator but may have caused a more marked decrease in systemic pressures. The possible effects of its metabolite, cyanide, on the mother and fetus should also be considered.

However, it is significant that after delivery of the infant and administration of a small dose of oxytocin, the response to GTN was less favourable and attempts at lowering pulmonary artery pressure were accompanied by unacceptable decreases in systemic arterial pressure. However, at this stage after delivery there are dramatic changes in fluid distribution and vascular resistance. We were unsure if this was an effect of oxytocin, changes in the vascular responsiveness to GTN or normal physiological changes. Substitution with prostacyclin was successful in restoring cardiovascular variables and underlines the need to prepare alternative dilator drugs. Prostacyclin was not used previously as we were concerned about its adverse haematological effects on the fetus. Prostacyclin is a potent vasodilator of all vascular beds. It causes relaxation of vascular smooth muscle by binding to its G protein-coupled receptor, activating adenylate cyclase and increasing production of cAMP. It is also a potent inhibitor of platelet aggregation, by increasing intracellular concentrations of cAMP. It has mild uterine relaxant properties. Prostacyclin has a short half-life in the circulation (2–3 min) and is hydrolysed rapidly at normal pH in the systemic circulation but not in its passage through the lungs. It has been used in intensive care in the management of primary and secondary pulmonary hypertension to improve cardiac performance and systemic oxygen delivery.[7]

Our previous experience of prostacyclin in patients with acute respiratory distress syndrome suggested that an infusion via the pulmonary flotation catheter might be useful. One of the theories on the pathophysiology of pulmonary hypertension is a mismatch of thromboxane–prostacyclin ratios in the lung endothelium.[4] The prostacyclin infusion had the desired effect, lowering pulmonary pressures and improving the cardiac indices. The postoperative bleeding which we encountered was assumed to be caused by the effects of prostacyclin on platelet aggregation. This is a short-lived effect, lasting 20–30 min. By replacing it with "aerosolized" prostacyclin, pulmonary pressure was controlled with minimal systemic effects.

Calcium antagonists were administered because they have been shown to increase survival of patients with pulmonary hypertension by 25%.[8] In view of the anticipated difficulties with weaning from artificial ventilation and to minimize "stress", the trachea was extubated on day 2 after operation while breathing spontaneously under sedation with propofol.

The patient was reviewed by the obstetrician and cardiologist and had an uneventful postpartum period. At 12 weeks after delivery and contrary to the strongest medical advice, the patient represented to the obstetric team, pregnant and at 4 weeks' gestation. She had a termination of pregnancy in the interest of maternal well being. The patient is still alive but complains of shortness of breath at rest.

References

1. Roberts NV, Keast PJ. Pulmonary hypertension and pregnancy—a lethal combination. *Anaesthesia and Intensive Care* 1990; **18**: 366–374.
2. Wilton NCT, Traber KB, Deschner LS. Anaesthetic management for Caesarean section in a patient with uncorrected truncus arteriosus. *British Journal of Anaesthesia* 1989; **62**: 434–438.
3. Roessler P, Lambert TF. Anaesthesia for Caesarean section in the presence of primary pulmonary hypertension. *Anaesthesia and Intensive Care* 1986; **14**: 317–320.
4. Rubin LJ. Pathology and pathophysiology of primary pulmonary hypertension. *American Journal of Cardiology* 1995; **75**: 51–54A.
5. Smedstad K, Cramb R, Morison D. Pulmonary hypertension and pregnancy: a series of eight cases. *Canadian Journal of Anaesthesia* 1994; **42**: 502–512.
6. Sandoval J, Bauerle O, Palomar A, Gomez A, Martinez-Guerra ML, Beltran M, Guerrero ML. Survival in primary pulmonary hypertension, validation of a prognostic equation. *Circulation* 1994; **89**: 1733–1744.
7. Bein T, Metz C, Keyl C, Sendtner E, Pfeifer M. Cardiovascular and pulmonary effects of aerosolised prostacyclin administration in severe respiratory failure using a ventilator nebulization system. *Journal of Cardiovascular Pharmacology* 1996; **27**: 583–586.
8. Rich S, Kaufmann E, Levy PS. The effects of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *New England Journal of Medicine* 1992; **32**: 76–81.

British Journal of Anaesthesia 1998; **81**: 793–794

Inadvertent inhalation anaesthesia during surgery under retrobulbar eye block

W. Q. Smith

Summary

I describe a case of inadvertent inhalation anaesthesia during surgery under retrobulbar anaesthesia and its management. Some of the hazards of supplementary oxygen delivery during monitored anaesthetic care and the actions taken to prevent this mishap recurring are discussed. (*Br. J. Anaesth.* 1998; **81**: 793–794).

Keywords: anaesthetic techniques, regional, retrobulbar; complications, apnoea; surgery, ophthalmological

Surgery under local anaesthesia is performed in many surgical disciplines and is common in ophthalmology. Despite the recent trend towards greater anaesthetic presence during this type of surgery, it still takes place in the absence of an anaesthetist. In these instances, it is recommended that an appropriately trained person, often the operating department assistant (ODA) or a theatre nurse, be present to monitor physiological variables such as arterial pressure, heart rate and oxygen saturation. I describe a case which underlines the constant dangers in an operating theatre environment when non-anaesthetic personnel are responsible for monitoring patients undergoing surgery under local anaesthesia in the absence of an anaesthetist.

Case report

An 83-yr-old woman presented for vitreoretinal surgery. The patient weighed 90 kg and was being treated for hypertension with slow release nifedipine 10 mg twice daily but had no history of cardiac failure or a cerebrovascular incident. Preoperative arterial pressure was 130/90 mm Hg, and heart rate was 50 beat min^{-1} and irregular, but there were no signs of cardiac failure. An electrocardiogram showed atrial flutter with variable atrioventricular block, a ventricular rate of 40–50 beat min^{-1} with left ventricular hypertrophy, and a normal axis. Haemoglobin and electrolyte concentrations, and a chest radiograph were within normal limits.

Having established i.v. access, a retrobulbar anaesthetic was administered by the consultant ophthalmologist using 0.75% bupivacaine 5 ml. After 15 min the patient's neck and face were covered with surgical drapes and surgery commenced. A theatre nurse sat beside the patient holding her hand and maintaining verbal contact. Monitoring included a three-lead ECG and pulse oximeter probe. Supplementary oxygen 4 litre min^{-1} was delivered via a Bain's breathing system attached to the anaesthetic machine and placed underneath the drapes near the patient's face. After a few minutes, verbal contact with the patient was lost and it was noticed that she had stopped breathing. The alarm was sounded and a consultant anaesthetist summoned from an adjacent theatre. The surgical drapes were removed and the airway supported.

On arrival, the anaesthetist found an unresponsive apnoeic patient, not cyanosed, with a heart rate of 40 beat min^{-1} and a weak pulse pressure. Oxygen was delivered by face mask via the same Bain's breathing system with airway support and manual inflation of the lungs. Atropine 600 μg was administered i.v. which increased heart rate to 80 beat min^{-1}. A non-invasive arterial pressure reading of 180/90 mm Hg was obtained. Oxygen saturation remained greater than 96% throughout. The patient began to breathe spontaneously but remained unresponsive with bilateral dilated pupils. A strong smell of isoflurane was noticed by the anaesthetist who found that the isoflurane vaporizer on the anaesthetic machine was switched to 5%. On discontinuing isoflurane, the patient awoke quickly and responded appropriately. There were no abnormal cranial nerve signs, except for the operated eye whose pupil had been dilated before operation with mydriatics.

Surgery was abandoned and the patient recovered normally. Subsequent follow-up revealed no abnormalities and she was discharged uneventfully to return for successful surgery a week later under retrobulbar anaesthesia.

Discussion

Apnoea after retrobulbar anaesthesia has been reported; it usually occurs within 8 min of injection, although onset has been delayed for up to 40 min.[1 2] Much is written about the contribution of technique, needle length and local anaesthetic concentration in producing brainstem anaesthesia as a cause of apnoea.[3–5]

On the initial assessment, it seemed very likely that the patient had suffered inadvertent subarachnoid injection with central spread of local anaesthetic. This is described as having an incidence of approximately 1 in 375.[6] However, the rapid and total recovery of the patient on removal of isoflurane, which is a potent cause of excessive sedation and possible apnoea, casts significant doubt on subarachnoid injection as the cause of this patient's misadventure.

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During administration of local anaesthetic blocks, patients may receive sedation and supplementary i.v. analgesia which can cause apnoea.[5] Monitoring oxygen saturation as a detector of respiratory inadequacy is widely accepted and advocated during surgery under local anaesthesia. In addition, the benefit of a dedicated nurse beside the patient maintaining verbal contact can result in very early detection of a problem, as demonstrated in this case.

The potential hazards of supplementing the patient's inspired oxygen concentration may not always be appreciated, especially when trained anaesthetic staff are not present. An editorial on the dangers of supplementary oxygen highlighted the hazards of inadvertent barotrauma when delivering oxygen from hyperbaric sources inappropriately.[7]

This case highlights the additional consideration of the safety of the inspired gas mixture during surgery under local anaesthesia. It is the responsibility of the anaesthetist, if present, to ensure that hypoxic or unsafe mixtures of gas are not inadvertently delivered to the patient. Older anaesthetic machines are often devoid of modifications which prevent the delivery of hypoxic gas mixtures. Such modifications include oxygen–nitrous oxide rotameter chain linkages and pneumatic mixing valves which guarantee a minimum of 25–30% inspired oxygen concentration.[8] Hypoxic guards deliver a constant minimum oxygen flow rate of 200 ml min^{-1} which is almost equivalent to adult basal oxygen consumption.

The anaesthetic machines in this eye hospital have cage mounted vaporizers which eliminates simple vaporizer removal from the bar, as with Selectatec mounted vaporizers, as a solution to inadvertent administration of volatile agent. On removal from the vaporizers, careful connection of appropriate tube ends is required with cage mounted vaporizer systems to ensure gas flow from the common gas outlet. Many anaesthetic machines still have carbon dioxide cylinders attached, creating the potential for inadvertent delivery of dangerous concentrations of carbon dioxide to a patient.

Clearly, human error resulted in failure to detect a vaporizer in the "on" position during supplementary oxygen delivery from the anaesthetic machine. It would not be reasonable to expect routine use of gas analysers by untrained personnel, which will detect the presence of volatile agent in inspired gas and hypoxic gas mixtures.

The importance of monitored anaesthetic care during local anaesthetic procedures, even in the absence of patient sedation or supplementary analgesia administration, is understated. It has been agreed by the Royal College of Anaesthetists and the College of Ophthalmologists that an anaesthetist is best suited for both administration of retrobulbar and peribulbar anaesthetics and intraoperative monitoring of the patient.[9] This standard for intraoperative monitoring is supported by the Association of Anaesthetists[10] and must be the ideal to strive towards in all hospitals. However, some patients are operated on under local anaesthesia in the absence of an anaesthetist. Recognizing that this practice, albeit undesirable, is endorsed for minor surgery in ophthalmology,[9] an alternative measure has been devised to allow safe delivery of supplementary oxygen in this eye hospital.

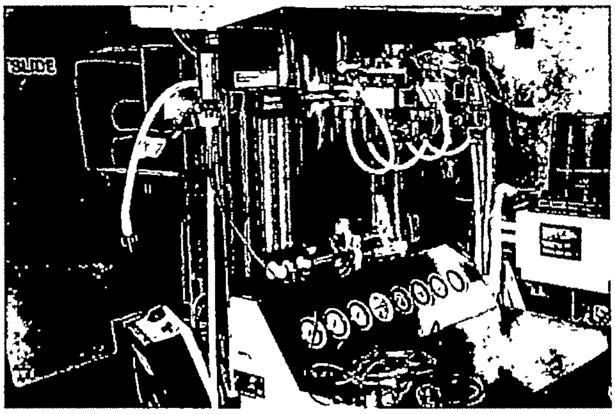

Figure 1 The oxygen flowmeter attached to a sidebar on the anaesthetic machine, with direct connection to piped oxygen, safely bypassing the rotameter system on the anaesthetic machine.

Bypassing the anaesthetic machine with an oxygen flowmeter directly connected to piped oxygen allows supplementary oxygen delivery to the patient via bubble tubing through either a conventional clear face mask or nasal cannulae. This has the advantage for non-anaesthetic personnel of avoiding the pitfalls in managing a rotameter system which delivers three or more gases, and has in-line vaporizers. In addition, there is no need for the use of an anaesthetic breathing system which may be incorrectly connected or faulty. By attaching the oxygen flowmeter to a bar on the side of the anaesthetic machine (fig. 1) it is not necessary to remove the anaesthetic machine permitting the use of integrated or attached anaesthetic monitors. It is simple and quick to modify the anaesthetic machine safely after general anaesthesia for use during local anaesthesia.

Surgery under local anaesthesia should ideally always be undertaken in the presence of an anaesthetist. Use of an anaesthetic machine by personnel unfamiliar with it is potentially hazardous.

References

1 Hamilton RC, Gimbel HV, Strunin L. Regional anaesthesia for 12 000 cataract extractions and intraocular lens implantation procedures. *Canadian Journal of Anaesthesia* 1988; **35**: 615–623.
2. Nicoll JM, Acharya PA, Ahlen K, Baguneid S, Edge KR. Central nervous system complications after 6000 retrobulbar blocks. *Anesthesia and Analgesia* 1987; **66**: 1298–1302.
3. Ahn JC, Stanley JA. Subarachnoid injection as a complication of retrobulbar anesthesia. *American Journal of Ophthalmology* 1987; **103**: 225–230.
4. Javitt JC, Addiego R, Friedberg HL, Libonati MM, Leahy JJ. Brainstem anesthesia after retrobulbar block. *Ophthalmology* 1987; **94**: 718–724.
5. Rigg JD, James RH. Apnoea after retrobulbar block *Anaesthesia* 1989; **44**: 26–27.
6. Rubin AP Complications of local anaesthesia for ophthalmic surgery. *British Journal of Anaesthesia* 1995; **75**: 93–96.
7. Newton NI. Supplementary oxygen—potential for disaster. *Anaesthesia* 1991; **46**: 905–906.
8. Parbrook GD, Davis PD, Parbrook EO. Volume and flow measurement. In. Parbrook GD, Davis PD, Parbrook EO, eds. *Basic Physics and Measurement in Anaesthesia.* Oxford: Butterworth-Heinemann, 1990; 29–43.
9. Report of the Joint Working Party on Anaesthesia in Ophthalmic Surgery. London: Royal College of Anaesthetists and College of Ophthalmologists, March 1993
10. Recommendations for Standards of Monitoring during Anaesthesia and Recovery. London: Association of Anaesthetists of Great Britain and Ireland, 1994 (revised)

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EQUIPMENT

Autoclaving impairs the connector–tube bond of the laryngeal mask airway but not its airtightness†

C. Preis, T. Hartmann, I. Preis, E. Wildling and H. Gilly

Summary

The general-purpose laryngeal mask airway (LMA) is re-usable when undamaged, and cleaned and autoclaved correctly. We had found weakening of the silicone adhesive that bonds the connector of the LMA to the tube. We report that repeated autoclaving damaged the adhesive such that the connector could be rotated in the tube after the 12th autoclave cycle in almost all of the LMA tested. The damage to the adhesive did not affect the airtightness of the junction, which appears to be maintained by the material properties of the connector and tube and by the shape of the join. (*Br. J. Anaesth.* 1998; **81**: 795–796).

Keywords: equipment, masks anaesthesia; airway, patency

The LMA has gained worldwide acceptance as a re-usable general purpose airway.[1] To determine the safety of the mask for re-use after cleaning and autoclaving, the anaesthetist must confirm the integrity of various parts of the mask in each of seven steps suggested by the manufacturer. The pass criterion of test 7, the focus of our study, is that the connector continues to "fit tightly into the outer end of the breathing tube and it should not be possible to pull it off".[2] To decide if a mask should be used, one should probably read the instruction as "pull it straight out," for reasons that are set forth in this article.

The mask is delivered unsterilized with the connector bonded to the tube by a silicone adhesive. After Zavattaro's letter on LMA failure,[3] we followed his recommendation to twist the tube of the LMA while examining masks for material softening to avoid accidental spiral tears of the tube. In doing so we noticed that, in some masks, even those autoclaved only a few times, the connector was no longer bonded to the tube, that is we could rotate the connector in the breathing tube and then twist the connector away from it. The adhesive bond between the connector and the tube seemed impaired by repeated autoclaving. Thus we designed two tests to determine how many autoclave cycles the adhesive bond would withstand and if impairment of the connector–tube adhesive bond reduces the airtightness of the LMA.

Materials and methods

We investigated 62 LMA taken from the original package. Six of the 62 could not be evaluated because twisting showed that the adhesive bond was already impaired and the connectors were detachable from the tube at the time the LMA were taken from the original package. The remaining 56 LMA were sterilized according to the instructions of the manufacturer[2] using a standard autoclave (Autoclav/Sterilisator ODELGA MJS04 WA#9589; Fa. KMB-ODELGA, Vienna, Austria; 121°C, 20 min). We autoclaved each LMA 15 times. To simulate clinical use, each was autoclaved at intervals of at least 24 h. After each autoclave cycle, we performed the seven mandated tests.

To identify the point at which it becomes possible to rotate the connector in the tube, that is the point at which the adhesive bond has become impaired, we designed a mechanical test to exert a defined, reproducible torque on the connector–tube bond of the 56 LMA. A torque wrench pre-set to a maximum force of 1 Newton metre (Nm) (approximately the force that a pair of hands of normal strength could apply) was used to twist the connector 180° while the tube was held still. In the second test, the airtightness of the junction between the breathing tube and connector was determined by an immersion trial: the tube of the LMA was blocked, immersed in water and connected to the hospital's central oxygen supply for oxygen flow. The pressure at which the device leaked, that is the pressure at which bubbles were detected, was noted. As flow continued, the pressure measured in the system increased to 120 cm H_2O.

Results

All evaluable 56 LMA passed tests 1–6 after each of the 15 autoclave cycles. With regard to test 7, it was not possible at any point in the autoclave cycle series to disconnect the connector from the tube by pulling it straight out. The torque wrench rotated the connector in the tube (i.e. rendered it detachable) in 52 of the 56 LMA (93%). All size 3 (n=18) and size 4 (n=14) LMA could be rotated after the third auto-

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clave cycle and all size 5 (n=13) LMA after the 12th autoclave cycle. The connectors could be rotated in seven of 11 paediatric size LMA (sizes 1–2.5) after the 14th autoclave cycle. In four other paediatric LMA, the connector–tube bond remained immovable even after 15 autoclave cycles (table 1). When the adhesive had failed, that is where it was possible to rotate the connector, we were able to twist the connector out of the tube.

The junction between the connector and breathing tube remained airtight. No air leakage was detected up to a pressure of 120 cm H_2O in any of the 56 LMA tested.

Table 1 Number of LMA with adhesive remaining intact, by autoclave cycle and size

No. of autoclave cycles	LMA size					
	Paediatric			Adult		
	Size 1	Size 2	Size 2.5	Size 3	Size 4	Size 5
0	2	5	4	18	14	13
1	2	5	3	13	12	13
2	2	5	3	8	3	13
3	1	5	3	0	0	13
4	0	5	3			13
5		5	3			12
6		4	2			5
7		4	2			3
8		3	2			2
9		3	2			1
10		3	2			1
11		3	2			1
12		3	2			0
13		3	2			
14		3	2			
15		3	1			

Discussion

We know of no reports in the literature of patient harm following separation of an LMA connector from the tube. Separation may occur and is mentioned in the manufacturer's manual. Our results clearly showed that most connectors become detachable after limited re-use of the mask and could be separated from the tube with a simple twisting motion. Anaesthetists need to be made aware of this, although loss of adhesion does not directly lead to detachment of the connector from the tube, and LMA with detachable connectors remain airtight. The continued tightness of fit is because of the shape of the connection and the materials of which the parts are made; however, these materials do not allow for a durable silicone-adhesive bond between the tube and connector, particularly in view of the temperatures associated with autoclaving (O. Seycek, Austrian Institute of Synthetics, Vienna, personal communication).

In different tracheal tubes, only the reinforced models have glued connectors similar to those of the new LMA. Standard tracheal tubes have a removable 15-mm connector which, in common with that of repeatedly autoclaved LMA, is not removable by pulling straight out, but is removable by twisting. Such tracheal tubes are often used with the patient in a prone or lateral position, or during ear, nose and throat surgery, when surgical drapes and the work of the surgeon make it more difficult for the anaesthetist to monitor continuously the integrity of the airway. Similarly, LMA prototypes were constructed from conventional 10-mm tracheal tubes[4] with a removable connector. During development and the preliminary trials of the LMA, neither loss of airtightness nor inadvertent disconnection attributable to the removable connector was reported.

We conclude that LMA are re-usable even with ineffective adhesive and even if the connector can be twisted out of the breathing tube, as long as it cannot be pulled straight out of the tube. This distinction is essential to the decision whether or not to discard or re-use a laryngeal mask airway.

References

1. Brimacombe JR, Berry A. The laryngeal mask airway—the first ten years. *Anaesthesia and Intensive Care* 1993; 21: 602–607.
2. Brain AIJ. *The Intavent Laryngeal Mask. Instruction Manual*, 2nd Edn, January 1993. Copyright Brain Medical Limited, October 1992.
3. Zavattaro M. LMA failure. *Anaesthesia and Intensive Care* 1996;24:119.
4. Brain AIJ, McGhee TD, McAteer EJ, Thomas A, Abu-Saad MA, Bushman JA The laryngeal mask airway. Development and preliminary trials of a new type of airway. *Anaesthesia* 1985;40:356–361.

British Journal of Anaesthesia 1998; **81**: 797

CITATION CLASSIC

Commentary

Shapiro HM, Galindo A, Wyte SR, Harris AB. Rapid intraoperative reduction of intracranial pressure with thiopentone. *British Journal of Anaesthesia* 1973; **45**: 1057–1062.

Classically, clinicians tended to avoid the use of drugs which depress the central nervous system in patients with evident neurological dysfunction. Clearly, therefore, the deliberate administration of a barbiturate (thiopental) to a variety of patients with intracranial pathology, some of whom had marked increases in baseline intracranial pressure, was a significant departure from the norm. Fortunately, Shapiro and colleagues were able to demonstrate that bolus doses of thiopental 1.5–3.0 mg kg^{-1} decreased intracranial hypertension and modified rapidly, acutely-induced increases in intracranial pressure in the peroperative period. In this way they, probably more than any other group, advanced a role for the barbiturates which has continued to the present time.

In more recent times it became fashionable to debate the rationale of the measurement and manipulation of intracranial pressure and hence the value of seeking to decrease intracranial hypertension *per se*. Such discussion was not an issue at the time Shapiro and colleagues were undertaking this and other related studies. Intuitively, it seemed reasonable to conclude that evident intracranial hypertension was potentially dangerous in patients with established intracranial pathology[1] and that acute increases, even if relatively brief, could be disadvantageous in those patients in whom intracranial compliance was reduced.[2] Quite simply, any increase in intracranial pressure to above the accepted upper limit of normal (25 mm Hg at that time) could be shown to decrease calculated cerebral perfusion pressure (in the absence of any compensatory increase in mean arterial pressure) with the possibility of an associated decrease in cerebral tissue blood flow and hence delivery of the required energy-generating substrates. In patients with neurological dysfunction, prevention of or, when possible, reversal of secondary brain damage was the ultimate goal: the control of respiratory variables, and of systemic and intracranial pressures, were the therapeutic challenges.

Modulation of intracranial pressure was achieved in several centres by meticulous application of a therapeutic regimen which included careful positioning of the head and neck, hyperventilation (facilitated by neuromuscular block), osmotherapy, prevention of hyperthermia, administration of corticosteroids and, if appropriate, drainage of cerebrospinal fluid. The introduction of barbiturate therapy was seen as an exciting, and potentially valuable, addition to the clinician's armamentarium. The intervening years have seen the case against the use of corticosteroids (at least in the head-injured patient) supported, the role of hyperventilation re-assessed and the place of hypothermia (at least "mild" hypothermia) re-established. With time, the place of the barbiturates in the management of intractable intracranial hypertension, and in the treatment of patients with focal ischaemia, has been clarified.

In highlighting these issues it could be argued that I have strayed from the basis of the cited article as that dealt exclusively with the effects of *intraoperative* administration of thiopental. However, I submit that this has been justified on two counts. First, it is likely that some of the patients had suffered from a head injury, although this is not stated explicitly. Second, I feel that to consider this 1973 article on its own robs it of much of its significance. In a subsequent article,[3] the same group demonstrated that administration of a barbiturate (pentobarbital) decreased persistently increased intracranial pressure when given to patients with a head injury. In other words, when considered together, these two studies demonstrate the potential contribution of administration of a barbiturate to modulation of intracranial pressure both in the operating theatre and in the intensive care arena. Clearly, these were not the first occasions in which a barbiturate had been given to modify intracranial pressure or dural tension. However, I believe that they were the first to bring together the three fundamental issues which gave validity to the investigations: accurate measurement of *intracranial* pressure, *deliberate* administration of the test agent in an attempt to decrease the increases in pressure and, very importantly, measurement of the induced changes in systemic arterial and calculated cerebral perfusion pressures. As such, this was a significant milestone in the management of patients with intracranial hypertension and in the possible part the barbiturates, or other drugs with similar properties, could play in patients with neurological dysfunction.

In the concluding sentence of their 1973 article the authors state that: "The ...... properties of thiopentone suggest that it warrants ..... selective application in the control of intracranial hypertension". I submit that this statement is as valid today as it was when published 25 yr ago.

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References

1. Graham DI, Adams JH. Ischaemic brain damage in fatal head injuries. *Lancet* 1971; **1**: 265–266.
2. Fitch W, McDowall DG Effect of halothane on intracranial pressure gradients in the presence of intracranial space-occupying lesions. *British Journal of Anaesthesia* 1971; 43 904–912
3. Shapiro HM, Wyte SR, Loeser J. Barbiturate-augmented hypothermia for reduction of persistent intracranial hypertension. *Journal of Neurosurgery* 1974; 40· 90–100.

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Brit. J. Anaesth. (1973), **45**, 1057

RAPID INTRAOPERATIVE REDUCTION OF INTRACRANIAL PRESSURE WITH THIOPENTONE

H. M. SHAPIRO, A. GALINDO, S. R. WYTE AND A. B. HARRIS

SUMMARY

Thiopentone was administered in bolus doses (1.5–3.0 mg/kg) 26 times to 18 neurosurgical patients undergoing craniotomy. Intracranial pressure and blood pressure responses to thiopentone were evaluated and the cerebral perfusion pressure calculated. Thiopentone given 21 times to treat chronic or acutely elevated intracranial pressure significantly reduced the mean pressure from 40 ± 1.5 to 22 ± 1.4 mm Hg (± SD). During these 21 treatments the cerebral perfusion pressure increased in 15, remained stable in 2 and decreased in 3. With induction of anaesthesia in patients with normal pre-thiopentone pressures, the barbiturate produced no significant alteration in intracranial pressure and the cerebral perfusion pressure remained above 85 mm Hg despite moderate reductions in arterial pressure. Frequently the action of the short-acting barbiturate in reducing intracranial pressure was transient, being limited, presumably, by redistribution of the drug.

Certain anaesthetic agents, and some types of stimulation during operation cause rapid increased intracranial pressure in neurosurgical patients. Elevations of pressure may follow noxious stimuli such as laryngoscopy, intubation, application of a head clamp, skin incision (Shapiro et al., 1972b), or follow administration of certain anaesthetic agents (Jennett et al., 1969; Shapiro, Wyte and Harris, 1972). Spontaneous increases of intracranial pressure have also been reported (Lundberg, 1960). These elevations may be sufficient to establish gradients of intracranial pressure leading to brain shifts (Fitch and McDowall, 1971), tissue compression and regional and/or total cerebral blood flow reduction (Zwetnow, 1970). During anaesthesia, reduction of the inspired concentration of the volatile agent or the administration of an osmotic dehydrating agent may not block or decrease a rapidly increasing intracranial pressure. Hyperventilation can, by decreasing the arterial carbon dioxide tension, often rapidly reduce an elevated pressure. Unfortunately, absolute control of the airway and ventilation is not always possible during anaesthetic induction. Ventricular cerebrospinal fluid removal can also rapidly lower intracranial pressure. However, this method is not always feasible and, when available, the ventricular catheter may become occluded when most needed. It is desirable, therefore, to have an agent that can be injected intravenously in order to obtain control when a sudden rise in intracranial tension occurs.

Thiopentone increases cerebral vascular resistance, decreases cerebral blood flow and the cerebral metabolic rate (Pierce et al., 1962). Theoretically these properties might be used to produce a rapid reduction of acute intracranial hypertension caused by cerebrovascular dilatation and increased intracranial blood volume (Risberg, Lundberg and Ingvar, 1969). We have evaluated the efficacy of thiopentone treatment for increased intracranial pressure in patients undergoing craniotomy under several types of anaesthetics.

METHODS

Intracranial pressure was continuously monitored in 18 neurosurgical patients before and after the induction of anaesthesia. The pressure was monitored

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through an intraventricular cannula or via a 19-gauge scalp-vein needle inserted into the dome of a valveless shunt prosthesis with its distal end occluded. The aetiology of the central nervous system lesion was tumour, subarachnoid haemorrhage, primary hydrocephalus, cerebral contusion, or non-space-occupying seizure focus.

Arterial blood pressure was measured either with a brachial cuff or through a radial artery catheter. All measurements were performed with the patients supine. In 14 patients the arterial pressure as well as central venous pressure and end-tidal carbon dioxide concentration were continuously monitored. Pressures are reported as the arithmetic mean of the systolic and diastolic values. Cerebral perfusion pressures were determined by subtraction of the mean intracranial pressure from the mean arterial pressure. A change of more than 2 mm Hg (27 mm H_2O) in intracranial pressure or calculated cerebral perfusion pressure was considered significant for the purposes of this report.

Either no medication or atropine 0.3–0.5 mg was given 1 hour before induction of anaesthesia. The anaesthetic protocols were varied in order to compare a volatile anaesthetic technique with one avoiding the use of halothane. In patients 1 through 9 anaesthesia was induced with thiopentone 1.5–3.0 mg/kg and maintained with halothane, nitrous oxide 3 l./min and oxygen 2 l./min. Patients 10 through 18 were given droperidol 100 μg/kg followed in 5 minutes by fentanyl 5–10 μg/kg and tubocurarine 0.35–0.45 mg/kg. This was followed by thiopentone 1.5–3.0 mg/kg and anaesthesia was maintained with nitrous oxide 3 l./min and oxygen 2 l./min. Thiopentone induction data were not available for patients 16 and 18.

Thiopentone was given to treat an increase in intracranial pressure in three situations: (1) for induction of anaesthesia; (2) during a period of rapidly rising pressure; and (3) at an elevated pressure following a rapid rise. For the purpose of this report an increase in intracranial pressure is defined as an intracranial tension gain of 10 mm Hg or more in 60 seconds. A pressure reduction response attributed to thiopentone was required to begin within 60 seconds following a bolus dose of the barbiturate and to cause a decline of more than a 2 mm Hg in intracranial tension. This corresponds with the period of brain thiopentone uptake and time of greatest anaesthetic depth (Price, Dundee and Conner, 1957). The lowest pressure obtained within 5 minutes of the administration of thiopentone is reported. By this time the brain concentration of thiopentone has decreased by 50% (Price, Dundee and Conner, 1957). During this observation period the patients were breathing spontaneously prior to anaesthetic induction, or ventilation was controlled at a constant rate. Hyperventilation was not initiated during the period of thiopentone evaluation.

An assignment to a response type based on the pre- and post-thiopentone intracranial pressure and cerebral perfusion pressure relationship was performed. Table II contains the definition of these relationships. Utilization of the cerebral pressure permits classification of the intracranial pressure response to a treatment relative to arterial pressure changes. The intracranial pressure was regarded as abnormally high if it exceeded 10 mm Hg, in accordance with Lundberg's (1960) definition.

RESULTS

Thiopentone in bolus doses significantly ($P<0.001$) reduced the average intracranial pressure from 40 ± 1.5 mm Hg ($\pm$SD) to 22 ± 1.4 mm Hg on 21 occasions when given to 13 patients with chronically elevated intracranial pressures (induction studies) or during episodes of acute intraoperative intracranial hypertension. The example in figure 1 represents a

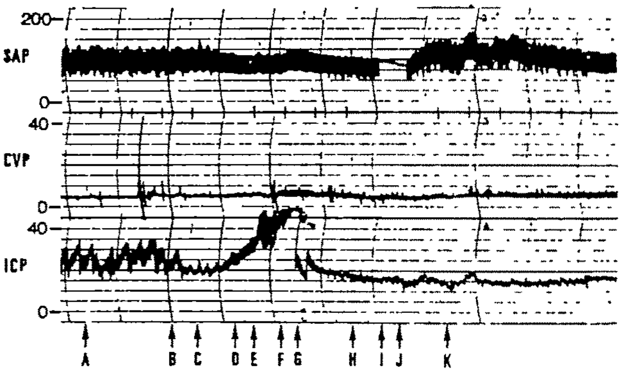

FIG. 1. Typical intracranial pressure reduction response to thiopentone during induction of anaesthesia. Event code as follows:

A	Oxygen by facepiece
B	Fentanyl 0.05 mg
C	Fentanyl 0.05 mg followed by tubocurarine 3 mg
D	Fentanyl 0.05 mg
E	Tubocurarine 12 mg
F	Thiopentone 200 mg (intracranial pressure trace exceeded calibrated scale and abruptly dropped after barbiturate administration)
G	Tubocurarine 12 mg
H	Tubocurarine 6 mg
I	Pa_{O_2} 480, Pa_{CO_2} 26 mm Hg
J	Laryngoscopy
K	Intubation complete
SAP	= systemic arterial pressure
CVP	= central venous pressure
ICP	= intracranial pressure

Time in minutes noted below SAP trace.

typical example of the response to thiopentone following an abrupt rise in pressure during induction of anaesthesia with droperidol and fentanyl. Table I gives the intracranial, arterial and calculated cerebral perfusion pressure values after a rapid intravenous dose of thiopentone.

TABLE I. *Changes in mean intracranial, arterial and cerebral perfusion pressures before and after administration of thiopentone.**

	Intracranial pressure		Arterial pressure		Cerebral perfusion pressure	
	Before	After	Before	After	change	Response type
			INDUCTION			
1a	2	2	121	100	−21	IV
2	8	7	162	158	−3	IV
3	14	13	124	122	−1	VI
4	6	5	160	138	−21	IV
5	7	6	150	98	−51	IV
6	9	6	122	103	−16	III
7	22	12	88	72	−6	III
8	34	20	120	55	−51	III
9a	14	13	66	68	+3	V
10a	46	18	102	95	+21	I
11	50	20	100	88	+19	I
12a	50	36	95	93	+12	I
13	40	25	95	90	+10	I
			INTRAOPERATIVE			
1b	24	8	178	125	−37	III
1c	25	16	102	105	+12	I
1d	39	33	108	101	−1	II
9b	38	18	68	72	+24	I
10b	44	16	95	90	+46	I
12b	50	40	88	86	+8	I
12c	64	45	90	88	+17	I
14	46	30	80	62	−2	II
15	11	5	80	92	+18	I
16	62	40	83	88	+27	I
			HALOTHANE			
1	38	15	104	112	+31	I
17	61	10	85	91	+57	I
18	40	16	100	90	+14	I

*Eighteen patients were evaluated; some during more than one episode of intracranial hypertension.

Considering all thiopentone treatments given to patients with abnormally elevated intracranial pressure (<10 mm Hg), we found that the pressure declined in 19 of 21 (95%) drug trials (table II). In 14 of these 21 trials (70%) the calculated cerebral perfusion pressure increased, in some instances from below to over 50 mm Hg. It fell in 15% of treated patients with high intracranial pressure, and all 5 patients with normal preanaesthetic intracranial tension. The perfusion pressure for all treated patients remained at 60 mm Hg or more, except for one patient, in whom it decreased to 35 mm Hg due to arterial hypotension.

TABLE II. *Distribution of intracranial and cerebral perfusion pressure responses to thiopentone injection in patients with preoperatively elevated and normal intracranial pressures.*

Response type	ICP	CPP	Elevated ICP mm Hg (n=21)	Normal ICP<10 mm Hg (n=5)
I	↓(P<0.001)	↑(P<0.001)	14	0
II	↓	—	2	0
III	↓	↓	3*	1
IV	—	↓	0	4**
V	—	↑	1	0
VI	—	—	1	0

Number of patients in each class are noted. Bracketed values indicate the results of the matched pair t-test applied to class I responses only. Significance relates to the direction of change of each variable from pretreatment values. Statistical tests in the other groups were omitted because of the small n.

*CPP below 50 mm Hg in one patient, above 60 mm Hg in other three.

**CPP above 85 mm Hg in all cases.

In patients with normal preoperative intracranial tension (<10 mm Hg), thiopentone had its greatest effect on arterial pressure, and, therefore, on cerebral perfusion pressure, and had little influence on intracranial pressure. These changes were noted during the induction of anaesthesia (fig. 2, right lower cluster of arrows, excluding response 3) and represent type III or IV responses. In no instance did the perfusion pressure fall below 90 mm Hg in these patients. Figure 2 also illustrates the efficacy of thiopentone in reducing an abnormally elevated intracranial pressure existing before anaesthesia (left upper cluster). There were four responses (fig. 2) leading to a reduction in intracranial pressure with improvement in the perfusion pressure in patients with high intracranial pressure as determined by preoperative measurement.

Thiopentone administered after the onset of an acute intracranial pressure wave caused by intraoperative noxious stimuli or inhalation of halothane quickly diminished the pressure (fig. 3). The cerebral perfusion pressure was frequently much improved by these treatments.

When thiopentone was given to control elevated intracranial pressure caused by halothane, the duration of the pressure reduction was transient, lasting only from 3 to 7 minutes. Supplementary thiopentone administration could maintain a reduced pressure in this situation, as the inspired concentration of halothane remained constant. The reduction in intracranial pressure achieved with thiopentone after

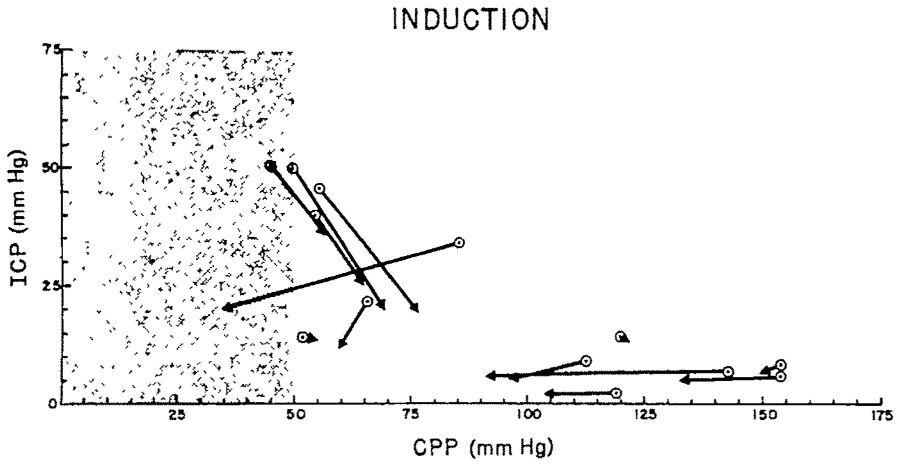

FIG. 2. Relationship of the ICP to CPP before and after the induction of anaesthesia with thiopentone. In this and the following figure the tail of the arrow indicates the prevailing ICP-CPP relationship prior to thiopentone administration and the head of the arrow represents the post-treatment values. The shaded area indicates the critical cerebral blood flow range wherein autoregulation fails.

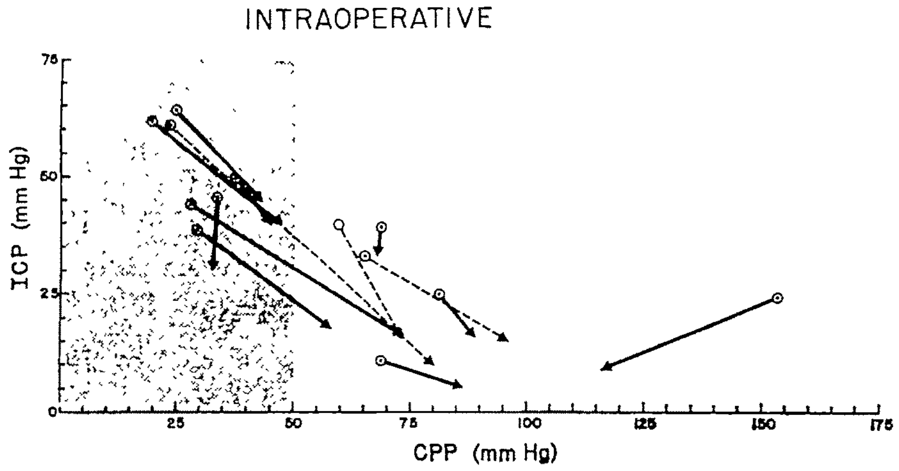

FIG. 3. Relationship of the ICP to CPP during or after a rapid increase in the ICP due to intraoperative stimuli (solid lines) or halothane (dashed lines) and after treatment with thiopentone.

intraoperative mechanical stimulation was longer lasting. Thiopentone never increased the intracranial pressure and there was no abrupt change in the central venous pressure or end-tidal carbon dioxide concentration consequent upon its administration. When intermittently sampled, the arterial carbon dioxide tension ranged between 23 and 32 mm Hg during controlled ventilation. The anaesthetic technique did not appear to alter the intracranial pressure response to thiopentone.

DISCUSSION

Continuous monitoring of intracranial pressure during anaesthesia in neurosurgical patients provides an improved basis for testing therapeutic manoeuvres directed at the maintenance of intracranial homeostasis. Monitoring of the arterial pressure, pulse rate, and respiration is not sufficient to estimate the degree of cerebral circulatory impairment during stressful events, nor does it enable an assessment to be made of the magnitude of intracranial pressure gradients (Heilbrun, Balslev and Boysen, 1972). Since a generally parallel relationship between cerebral blood flow and cerebral perfusion pressure exists when the perfusion pressure falls below 30 to 50 mm Hg (Heilbrun, Balslev and Boysen, 1972; Zwetnow, 1970), measurement of the intracranial and arterial pressures can provide information relating to cerebral blood flow. A perfusion pressure below 50 mm Hg may be a warning of present or impending cerebral circulatory impairment, and regional perfusion pressures (about a mass lesion) could be even more dangerously reduced.

In 1937 Horsley found minor reductions in lumbar cerebrospinal fluid pressure during barbitone narcosis in 100 normal volunteers. Shortly thereafter this observation was confined by Gurdjian, Webster and Sprunk, (1939). They also noted that pentobarbitone did not increase spinal fluid pressure when used for sedation in restless head injured patients in the absence of airway obstruction. Søndergard (1961) measured intracranial pressure during general anaesthesia in eight neurosurgical patients and observed reductions in intracranial tension during induction of anaesthesia with thiopentone or pentobarbitone (Søndergard, 1961). Hunter (1972) has advocated the use of thiopentone supplemented anaesthesia (continuous intravenous infusion) for neurosurgery. He observed the curvature of the dural surface and reported "excellent" to "good" dural relaxation in a high percentage of his patients. In a preliminary report, we noted the ability of thiopentone to reduce acutely elevated intracranial pressure during operation (Shapiro et al., 1972a). Intracranial hypertension caused by ketamine can also be reversed by thiopentone injection (Shapiro, Wyte and Harris, 1972).

Our present study confirms the ability of thiopentone to reduce chronically (induction responses) and acutely elevated intracranial pressure. Therefore, thiopentone treatment may abort incipient intracranial tissue herniation due to a rapidly expanding intracranial blood volume. Additionally, we found that this short-acting barbiturate frequently improved the cerebral perfusion pressure gradient and could quickly antagonize acute rises of intracranial pressure caused by halothane administration.

Although thiopentone reduces cerebral blood flow in normal persons (Pierce et al., 1962), it could, potentially, improve regional or total cerebral perfusion in cases of acutely elevated intracranial pressure due to cerebrovasodilatation and augmentation of cerebral blood volume. In this situation, constriction of the cerebral vessels by thiopentone could reduce the intracranial blood volume (a high volume may be stagnant and not represent flow) and intracranial pressure. Then the resistance to flow exerted by the thiopentone-constricted vessels might be less than that due to the high intracranial pressure, and cerebral blood flow could increase. There are no studies confirming this concept.

The transient nature of the reduction in intracranial pressure, obtained with thiopentone, given to control pressure increases caused by halothane and ketamine is probably explained by the rapid reduction in cerebral thiopentone levels after injection of a bolus dose (Price, Dundee and Conner, 1957), as well as by the continued cerebrovasodilator effects of the anaesthetic agents studied. More prolonged intracranial pressure decreases with thiopentone appear possible if the maximal stimuli increasing the pressure are transient, such as tracheal intubation or incision of the skin. Maintenance of a reduced pressure after treatment of acute intracranial hypertension with thiopentone may possibly be achieved with hyperventilation. The increased cerebrovascular resistance caused by reduced arterial carbon dioxide tension (Reivich, 1964) may supplement further thiopentone treatments. The effect of a combined thiopentone-hypocapnic treatment on intracranial pressure was not evaluated in this study, except insofar as the arterial carbon dioxide tension was generally below normal. Finally, reduction of the cerebral metabolic rate by thiopentone may offer some protection against cerebral ischaemia (Nilsson, 1971) caused by high intracranial pressures. The metabolic and cerebrovasoactive properties of thiopentone suggest that it warrants further selective application in the control of intracranial hypertension.

REFERENCES

Fitch, W., and McDowall, D. G. (1971). Effect of halothane on intracranial pressure gradients in the presence of intracranial space-occupying lesions. *Brit J. Anaesth.*, **43**, 904.

Gurdjian, E. S., Webster, J. E., and Sprunk, C. J. (1939). Studies of the spinal fluid in cases of injury to the head. *Arch. Neurol. Psychiat. (Chicago)*, **42**, 92.

Heilbrun, M. P., Balslev, P., and Boysen, G. (1972). Relationships between cerebral perfusion pressure and regional cerebral blood flow in patients with severe neurological disorders. *Stroke*, **3**, 181.

Horsley, J. (1937). The intracranial pressure during barbital narcosis. *Lancet*, **232**, 141.

Hunter, A. R. (1972). Thiopentone supplemented anaesthesia for neurosurgery. *Brit. J. Anaesth.*, **44**, 506.

Jennett, W. B., Barker, J., Fitch, W., and McDowall, D. G. (1969). Effect of anaesthesia on intracranial pressure in patients with space-occupying lesions. *Lancet*, **1**, 61.

Lundberg, N. (1960). Continuous recording and control of ventricular fluid pressure in neurosurgical practice. *Acta psychiat. scand.*, **36**, Suppl. 149, 1.

Nilsson, L. (1971). The influence of barbiturate anaesthesia upon the energy state and upon acid-base parameters of the brain in arterial hypotension and in asphyxia. *Acta neurol. scand.*, **47**, 233.

Pierce, E. C., jr, Lambertsen, C. J., Deutsch, S., Chase, P. E., Linde, H. W., Dripps, R. D., and Price, H. L. (1962). Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. *J. clin. Invest.*, **41**, 1664.

Price, H. L., Dundee, J. W., and Conner, E. H. (1957). Rates of uptake and releases of thiopental by human brain; relation of kinetics of thiopental anesthesia. *Anesthesiology*, **18**, 171.

Reivich, M. (1964). Arterial P_{CO_2} and cerebral hemodynamics. *Amer. J. Physiol.*, **206**, 25.

Risberg, J., Lundberg, N., and Ingvar, D. H. (1969). Regional cerebral blood volume during acute transient rises in the intracranial pressure. *J. Neurosurg.*, **31**, 303.

Shapiro, H. M., Galindo, A., Wyte, S. R., and Harris, A. B. (1972a). Acute intracranial hypertension during anesthetic induction: partial control with thiopental. *Europ. J. Neurol.*, **8**, 118.

—— Wyte, S. R., and Harris, A. B. (1972). Ketamine anaesthesia in patients with intracranial pathology. *Brit. J. Anaesth.*, **44**, 1200.

Shapiro, H. M., Wyte, S. R., Harris, A. B., and Galindo, A. (1972b). Acute intraoperative intracranial hypertension in neurosurgical patients: mechanical and pharmacologic factors. *Anesthesiology*, **37**, 399.

Søndergard, W. (1961). Intracranial pressure during general anaesthesia. *Dan. med. Bull.*, **8**, 18.

Zwetnow, N. N. (1970). Effects of increased cerebrospinal fluid pressure on the blood flow and on the energy metabolism of the brain: an experimental study. *Acta physiol. scand.*, **339**, (Suppl.) 1.

CORRESPONDENCE

SIMPLE AND RELIABLE METHOD OF INSERTING A NASOGASTRIC TUBE DURING ANAESTHESIA

Sir,—The communications of Matsuki and Zsigmond (*Brit. J. Anaesth.* (1972), **44**, 610) and Wedley (*Brit. J. Anaesth.* (1972), **44**, 1117) on the insertion of a nasogastric tube during anaesthesia are timely and the methods suggested helpful. So is the communication of Virtue (*Brit. J. Anaesth.* (1973), **45**, 234) which suggests a method for insertion of a nasogastric tube for those not musically inclined or equipped with guitar strings. However, I would like to suggest a further simplification of the method given by Dr Virtue. There is no need to slit any portion of the lesser curvature of a non-cuffed tracheal tube. The nasogastric tube to be passed is well lubricated and inserted into the tracheal tube till the distal end of the former is flush with the bevel of the tracheal tube or just inside it. The two are held together at the non-bevelled end of the tube. The distal portion of the tracheal tube is well lubricated and inserted through the nose into the oesophagus. The nasogastric tube is then threaded in till it reaches the stomach when the tracheal tube is threaded out.

A difficulty in the method suggested by Dr Virtue is that sometimes after passing the tracheal tube, the subsequent passage of the nasogastric tube may not be easy.

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THE EFFECTS OF ANAESTHETICS ON SPLANCHNIC CIRCULATION

Sir,—The article by L. H. Cooperman (*Brit. J. Anaesth.* (1972), **44**, 967) stimulates me to set forth several considerations derived mainly from animal experiments.

It is doubtful whether it is justifiable to discuss the question of changes in the hepatic circulation under the influence of anaesthetics by considering the total hepatic blood flow only, without taking into account the separate proportion of arterial and portal pathways.

My experimental investigations with direct measurement of hepatic blood outflow volume, and also with contrast X-ray angiocinematography, showed that halothane and ether decrease total hepatic blood flow to 60% of the initial values and reduce portal blood flow from 32.8 ± 1.6 to 14.1 ± 1.8 ml/min/100 g of liver (halothane) or from 37.6 ± 4.0 to 13.4 ± 1.0 ml/min/100 g (ether). At the same time the hepatic arterial blood flow increased by 30% in the case of halothane (from 7.9 ± 0.6 to 10.3 ± 1.1 ml/min/100 g), and by 59% with ether (from 8.7 ± 0.6 to 13.8 ± 1.1 ml/min/100 g).

Thus, the share of arterial flow in the total liver blood supply increases by more than twice. It is evident that, in conditions of anaesthesia leading to a decrease of hepatic blood flow, oxygenation of hepatic tissue is carried out by a marked arterialization of hepatic sinusoid blood. This reaction apparently contributes to the preservation of hepatocyte viability, but it is carried out to the detriment of other splanchnic system organs, which suffer circulatory hypoxia.

It is interesting to note that ganglionic blockade with pendiomid, reducing arterial pressure from 135 ± 4.7 to 108 ± 6.5 mm Hg, considerably increased hepatic artery blood flow (from 8.1 ± 0.4 to 14.6 ± 1.2 ml/min/100 g), and to a lesser degree the portal vein blood flow (from 36.1 ± 1.7 to 42.8 ± 0.8 ml/min/100 g). A more pronounced decrease of arterial pressure leads, primarily, to a fall in portal venous flow, while a reduction in the arterial blood flow is observed only when arterial pressure is less than 65–70 mm Hg.

The question whether it is possible to correct hepatic circulation disturbances during anaesthesia is important in practice. Dr Cooperman writes about only one of the possibilities, the increase in total hepatic blood flow with ganglionic blockade with a background of cyclopropane anaesthesia. We obtained similar results during ether anaesthesia. Also, the administration of oxygen into the lumen of the gastrointestinal tract, in 14 patients during abdominal operations, led to an increase in oxygen saturation of the portal vein blood from 55 ± 7.2 to 80 ± 6.2% and was accompanied by a decrease in the portocaval gradient from 74 ± 12.5 to 38 ± 8.7 mm H_2O. Experimentally, this method increased liver oxygen tension and portal blood flow twofold, by decreasing vessel resistance in the liver region of the portal bed.

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ABSTRACTS

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(The name of the presenting author is shown in bold type.)

Impact of opening a high dependency unit on the relative cost of living on intensive care

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The role of a high dependency unit (HDU) is to provide an environment within the hospital where patients are offered a standard of care between the general ward and the intensive care unit (ICU). HDU patients are far less likely than ICU patients to require costly multi-organ support.

Towards the end of 1997 we received funding to open a four-bed high dependency unit. We opted to closely audit the impact of this on the cost of patient treatment on the intensive care unit. In group 1, we studied consecutive patients admitted to intensive care for 8 weeks before the opening of the HDU; group 2 comprised consecutive patients admitted to the ICU after the opening of the HDU

Length of stay (LOS), admission APACHE II score, TISS score and outcome were collected for all patients. Daily TISS scores followed a normal distribution; all other data were analysed using non-parametric statistics (table 1). In 1986, Sage, Rosenthal and Silverman examined a subgroup of intensive care patients and found that the cost of dying was twice the cost of living; this has been reported by other authors.[1–3] We examined our *entire intensive care population* and confirmed this immediately before the opening of the HDU. Immediately after opening the HDU, mean TISS score of survivors in the ICU increased. If TISS reflects costs,[4] the cost of living now appeared to equal the cost of dying.

The cost of death remained the same after the opening of our HDU and efforts still need to be aimed at identifying those patients who are certain to die. We feel that rather than bemoaning the futility and expense of intensive care, we should appreciate that more than 75% of these expensive patients go on to survive.

Keywords: intensive care, audit

References

1. Sage WM, Rosenthal MH, Silverman JF. *Critical Care Medicine* 1986; 14: 777–782.
2. Bion J, Strunin L. *British Journal of Anaesthesia* 1996; 77: 1–2.
3. Atkinson S, Bihari D, Smithies M, Daly K. *Lancet* 1994; 334: 1203–1206.
4. Keene AR, Cullen DJ. *Critical Care Medicine* 1983; 11: 1–3.

Immediate impact of opening a high dependency unit on intensive care workload

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Availability in the high dependency unit (HDU) may reduce the number of premature discharges from the intensive care unit (ICU) to a ward, with the resultant large step down in the level of care.[1] Conversely, lack of HDU beds may mean that patients stay in the ICU longer than necessary.[2] Having previously audited the occupancy of our ICU, we now present results from a similar audit, which began on the day a new HDU was opened. We discuss the impact of HDU on the efficiency of use of intensive care resources.

Methods of calculating ICU occupancy are not consistent, making comparison between units difficult Some methods even result in occupancy figures of more than 100%. By using four different methods in our previous audit, we concluded that only hourly occupancy (i.e. number of patient-hours as a percentage of available bed-hours) gives a realistic result and, therefore, this is the method used here.

During each 8-week audit period, forms were completed daily based on the previous 24 h. Admission/discharge times were noted for hourly occupancy calculations. We used NHS Executive guidelines to define each patient as ICU or HDU status for each day of their admission, together with daily APACHE II and TISS scores (table 2). From 6 (+1) ICU beds, we now have 6 ICU and 4 HDU beds. We are able to have up to eight patients in the ICU by closing the HDU. Analysis of APACHE II and TISS scores confirmed that using NHS Executive guidelines to define patients as ICU or HDU status resulted in two distinct populations (P<0.0001).

Using the methodology of our studies, we have safely diverted funds from the ICU to the HDU The number of re-admissions to the ICU or HDU has fallen from 5 (of 60 discharged) to 0 (of 66 discharged) since the HDU opened. This significant decrease

Table 2 Hourly occupancy (number of patient-hours as a percentage of available bed-hours) in the intensive care (ITC) and high dependency (HDU) units

	Hourly occupancy (%)		
	ICU status	HDU status	Total
ICU 1st audit	63.7	21.6	85.3
ICU 2nd audit	73.4	11.2	84.6
HDU	0	50.4	50.4

Table 1 Length of stay (LOS), and APACHE and TISS scores in survivors and non-survivors, before and after the opening of the high dependency unit (HDU) (mean (SEM) or median (range)). *P=0.013

		n	TISS	APACHE	LOS (days)
Before HDU	Survivors	62	109.7 (20.5)*	12 (4–29)	1 (1–30)
	Non-survivors	16	242.8 (66.8)*	32 (18–40)	1.5 (1–19)
After HDU	Survivors	39	221.7 (52.8)	14 (4–30)	2 (1–33)
	Non-survivors	14	230.5 (52.3)	21 (10–48)	4.5 (1–25)

(P<0.05) supports the prediction that premature discharges would decrease. Occupancy of the ICU by HDU patients has halved but would be difficult to reduce further. All ICU survivors become HDU status for a period before leaving, and HDU patients requiring a side room (e.g. MRSA positive) have to stay in the ICU. Also, at times, the ICU can act as an overflow for the HDU if beds are available. Our HDU is adjacent to but separate from the ICU. While there is some flexibility in our use of the ICU and HDU beds, we suggest that a self-contained critical care unit would be even more efficient for the seamless care of patients. HDU hourly occupancy will always be lower than that in the ICU because of the faster turnover and, therefore, increased time that beds are empty. However, the low use revealed in our audit may reflect slow change in practice of surgeons, physicians and anaesthetists. We are aware that some patients electively booked into an ICU bed could have been re-directed to the HDU before leaving theatre if the possibility had been considered.

Keywords: intensive care, audit

References

1. Leeson-Payne CG, Aitkenhead AR. *Anaesthesia* 1995; 50: 383–387.
2. NHS Executive. *Department of Health Working Group Report*, 1996.

Secondary transport of critically ill obstetric patients

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Less than 1% of pregnant women ultimately require admission to an intensive care unit (ICU), but the need for admission may be unpredictable.[1] The majority of obstetric ICU admissions result from hypertensive disorders or haemorrhage. These problems accounted for 25 deaths in ICU in the latest *Confidential Enquiry into Maternal Deaths*.[2]

The Clinical Shock Study Group (CSSG) is based in Glasgow and provides a service for secondary transport of critically ill patients within the West of Scotland. We reviewed our obstetric transfers over the period 1992 to mid-1997.

Sixty-two patients were identified from CSSG records as being transferred from an obstetric unit to the ICU. The ICU notes for these transfers were consulted. Length of stay in the ICU for each patient was recorded and the severity of illness calculated using the APACHE II scoring system.[3] Forty-eight patients had either haemorrhage or hypertensive disorders, while the other 14 had a variety of problems, including pulmonary embolism and sepsis. Mann–Whitmey analysis revealed a significant difference only in length of stay in the ICU (P=0.026) (table 3).

Despite a clinical impression that there may be a difference between these groups, this only holds true for length of ICU stay. This may reflect the more complex, multi-system nature of hypertensive disorders, requiring a longer recovery period. With 20% of obstetric units on isolated sites, there is still a need for facilities to resuscitate and monitor these critically ill women before careful transfer to an intensive care unit.[4]

Table 3 Age, length of stay in the ICU and APACHE II score for obstetric patients transferred to the ICU (mean (range)). Significant difference in length of stay in the ICU (P=0.026; Mann–Whitmey)

	Age	ICU stay (days)	APACHE II
Haemorrhage (n=24)	31 (24–40)	1.8 (0.22–11)	10 (2–19)
Hypertension (n=24)	28.8 (21–35)	3.2 (0.5–20)	12.8 (3–26)

Keywords: intensive care, audit; pregnancy

References

1. Wheatley E, Farkas A, Watson D. *International Journal of Obstetric Anaesthesia* 1996; 5: 221–224.
2. *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1991–1993.* London: HMSO.
3. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. *Critical Care Medicine* 1985; 13: 818–829.
4. Cordingley J, Rubin AP. *International Journal of Obstetric Anaesthesia* 1997; 6: 156–160.

Implications of a change in operational policy

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Intensive care is not currently recognized as a speciality in the UK. As a consequence of this, in common with most other UK intensive care units (ICU), we traditionally left overall control of the patient with the admitting/referring clinician. Work in both adult[1,2] and paediatric units[3] has suggested that intensivists can improve outcome in intensive care. In mid-1994 the operational policy of our ICU was altered to give overall control to the ICU consultants. Therefore, we have analysed outcome data held on the ICU database to assess the impact, if any, of such a change.

Data held in the ICU audit database for the year before the change (1993) and the year after the change (1995) were analysed.

There was no difference in outcome between the 2 yr In 1993, predicted mortality was 26.1% and actual mortality 25.5% (SMR 0.98). In 1995, predicted mortality was 25.7% but actual mortality had reduced to 23.8% (SMR 0.93). Therefore, we examined stay in the ICU. The only change was in patients who died who stayed in the unit for less time (P=0.023). This was because of a marked reduction in duration of stay for those patients in whom active treatment was withdrawn from a median of 4 (2–9.5) days to 2 (1–5) days (P<0.0001).

It would appear that consultants in intensive care, when given overall clinical responsibility for patient care, are readier to withdraw active treatment than ward-based clinicians. Earlier identification of patients in whom death was inevitable and the subsequent change in direction of care (from active support aimed at survival, to palliative and compassionate care) has both ethical and financial consequences. Patients who ultimately suffer protracted deaths in the ICU consume a disproportionate amount of resources.[1]

Keywords: intensive care, audit

References

1. Reynolds N, Haupt MT, Thill-Baharozian MC, Carlson RW. *Journal of the American Medical Association* 1988; 260: 3446–3450.
2. Brown JJ, Sullivan G. *Chest* 1989; 96: 127–129.
3. Pollack MM, Cuerdon TT, Patel KM, Ruttiman UE, Getson PR, Levetown M. *Journal of the American Medical Association* 1994; 272: 941–946.
4. Atkinson A, Bihari D, Smithies M, Daley K, Mason R, McColl I. *Lancet* 1994; 344: 1203–1206.

Critical incident reporting in a district general hospital

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A critical incident may be defined as any incident which affected, or could have affected, the safety of a patient while under management of the intensive care unit. Critical incident reporting is designed to study the system, rather than individuals, and therefore must be completely anonymous. Its use in a large teaching institution has already been described.[1]

The critical incident form was developed by a group of intensive care nurses and piloted for 3 months before the study. The form was then modified (T. J. P.) and data transferred to a customized database (Access 2.0, Microsoft). We report the results of the first 13 months of this data collection in an eight-bed intensive care unit in a district general hospital (February 1, 1997 to February 28, 1998), representing 513 admissions. Broad categories only are presented. The database itself contains subdivisions within these categories.

Table 4 Critical incidents reported in the period February 1, 1997 to February 28, 1998

Place of occurrence	
In the intensive care unit	121
Internal hospital transfers	13
External hospital transfers	4
Patients referred in from outside	4
On the ward	1
In accident and emergency	1

Staff Involved (one or more)	
Consultant	24
Junior	33
Nursing	54
Technical	8
Others	23

Classification of causes of incidents (one or more)	
Management	64 (communication problems 48)
Equipment	67 (ventilation 18)
Patient care	57 (drug errors 36)
Hazards	19 (invasive lines 9)

Method of detection	
Direct observation	119
Invasive pressures	16
Pulse oximetry	4
Alarms	3
Laboratory results	2

Outcomes (one or more)		
Death	4	(no incident resulted directly in a patient's death)
Major physiological abnormality	11	(severe prolonged desaturation or hypotension)
Minor physiological abnormality	27	
No abnormality	57	
Staff dissatisfaction	67	
Staff injury	4	

A total of 144 critical incidents were reported; 116 were preventable, 125 involved human error and 69 were latent (system errors). The number per month varied from 6 (February 1998) to 17 (June 1997) with no clear seasonal pattern. Seventy-five incidents occurred between 08:00 and 17:00, and 69 outside these hours (table 4).

Critical incident analysis highlights problem areas for discussion at audit meetings, including mortality and morbidity. This facilitates the development of guidelines and risk management. The anonymous nature allows reporting of areas of interpersonal conflict and ethical dilemmas

Keywords: intensive care, audit

Reference

1. Buckley TA, Short TG, Rowbottom YM, Oh TE. *Anaesthesia* 1997; 52: 403–409.

Brain stem death and multi-organ donor management: a telephone survey of North West practice

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In the UK in 1997 the total waiting lists for cadaveric organ transplants out-stripped the completed transplants by more than 2500.[1] Thus it is imperative that patients put forward for organ donation are managed in such a way as to maximize the chances of successful recipient outcome. Such management should include the use of the pulmonary artery flotation catheter (PAFC) to monitor fluid and inotrope requirements in cardiac donors[2] and the use of hormonal manipulation to maintain end-organ function.[3] The aim of this telephone survey was to assess to what extent these goals are being achieved in the intensive care units (ICU) of North West England.

Consultants in 22 ICU were targeted over a 2-week period. A standard script using the case of a young healthy adult with an isolated but irrecoverable head injury was used If the first call was unsuccessful a second time was arranged. The following were assessed: (1) use of invasive monitoring in the given scenario; (2) implementation of additional monitoring in patients with brain stem death (BSD); (3) use of vasoactive drugs and hormone replacement in BSD patients; and (4) physiology of BSD: 10 true/false questions on the topic. A total of 22 units were contacted and 13 responded (11 consultants and 2 registrars) (table 5).

In the units which responded, there was a good deal of discrepancy in practice. The use of CVP and arterial lines (IABP) was universal. However, one-third of the units were not in the habit of considering the PAFC to facilitate fluid and inotrope use. Most units use, or consider using, inotropes and vasodilator drugs to ameliorate the response to BSD. Little over 50% use hormone replacement to preserve organ function. Many units indicated that their entire management was directed by the transplant co-ordinator (TC), although they admitted that the diagnosis of BSD had usually been made and hence the opportunity to smooth any CVS extremes had been missed, before involvement of the TC. The physiology questions, although not badly done, were completed correctly by only two units.

There are many pressures and constraints put in the ICU beds and, on the face of it, the time and money spent on the maintenance and aggressive management of organ donors is not always in the individual unit's interests. However, on a larger scale, the success of organ transplantation requires the individual unit to understand the process of BSD and to act appropriately to help give recipients the organs in the best possible condition.

Keywords: intensive care, audit; complications, brain stem death

References

1. United Kingdom Transplant Support Service Authority. Transplant Update. Data for Year ending 31/12/1997.
2. Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR. *Journal of Heart and Lung Transplantation* 1995; 14: 734–742.
3. Jeevanadam V, Todd H, Hellman S, Eldridge C, McClorken J, Addonizio VP. *Transplantation Proceedings* 1993; 25: 3305–3306.

Table 5 Survey of responses of the intensive care units on the monitoring/treatment of brain stem death

	Routine (%)	Consider (%)	Never (%)
Use of IABP and CVP lines	100	n/a	n/a
Use of PAFC	0	69	31
Use of PAFC post BSD	15	46	39
Use of inotropes	15	69	14
Use of hypotensives	15	61	24
Use of hormonal "cocktail"	15	38	47
True/false questions	max 10	min 4	mean 7

Caring for critically ill children in an adult intensive care unit

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The recent report from the National Co-ordinating Group on paediatric intensive care services[1] recommends that adult intensive care units (AICU) in district general hospitals restrict their paediatric activity to the initiation of intensive care before transfer of each child to a recognized centre. There was no outcome data quoted that supported this recommendation. We wish to report an ongoing outcome study concerning care of critically ill children on an AICU in a district general hospital.

All patients less than 16 yr of age admitted to the AICU at Southend General Hospital over a 4-yr period were identified. For each child, sex, age and length of stay were recorded. In addition the 14 physiological variables required to calculate the paediatric risk of mortality (PRISM) score were recorded on admission.[2] From this score the risk of death for each child was calculated. All children who had a low estimated mortality (less than 5%) and did not require specialist care (usually neurosurgery) were cared for locally. The estimated mortality of this group was compared with actual outcome.

Over a 4-yr period, 129 children were admitted. There were 63 girls and 66 boys aged 2 weeks to 15 yr (mean 61 months). Length of stay ranged from 2 h to 8 days (mean 41 h) and 83 children required mechanical ventilation. Calculated risk of death and observed mortality are shown in table 6.

Table 6 Calculated risk of death and outcome of children admitted to the adult intensive care unit

Risk of death	*n*	Deaths	Expected deaths
<1%	69	0	0.38
1–5%	43	0	0.8
5–10%	8	0	0.98
10–50%	5	0	0.43
>50%	4	2	2.21
Total	129	2	4.8

All 97 children with an estimated mortality of less than 5% who were cared for on the AICU survived. Thirty-two other patients were transferred after initial stabilization in our unit. PRISM scores gave an expected mortality of 4.8 patients but only two deaths were observed.

The observed mortality was less than that predicted. Our results suggest that an adult unit can provide an acceptable level of care for children with a low expected mortality. However, it is difficult to justify continuing to provide this care in view of the recommendations made by the National Co-ordinating Group on paediatric intensive care.

Keywords: intensive care, audit; children

References

1. *Paediatric Intensive Care. A Framework for the Future* Department of Health, 1997.
2. Pollack MM, Ruttiman UE, Getson PR. *Critical Care Medicine* 1988; **16**; 1110–1116.

A survey of neurosurgical transfers to a neurointensive care unit

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The guidelines "Recommendations for the Transfer of Patients with Acute Head Injuries to Neurosurgical Units"[1] were published in December 1996. We sought to characterize our neurosurgical transfers and to determine compliance with these guidelines.

All patients transferred to our neurosurgical intensive care unit since the start of 1998 were studied. The doctors responsible for the transfer answered a questionnaire by telephone.

Twenty-four transfers to the neurointensive care unit in a regional centre were studied; 58% were patients who had sustained head injuries while 42% had acute intracranial lesions needing transfer for specialist management. The average journey time was 35 min. Three transfers were by A&E doctors, while the rest were by anaesthetists, of which 66.6% had more than 2 yr anaesthetic experience. All had skilled assistance. The time spent preparing the patient (15–120 min) was mainly for intubation–ventilation, and insertion of venous and monitoring lines. Of the 22 intubated patients, 86% were intubated for decreased conscious level. A total of 75% of journeys were uneventful and any incidents during journey were mainly as a result of equipment failure and physiological changes. Propofol, midazolam, atracurium and vecuronium were popular for transfer. Most interventions during the journey involved drug administration of neuromuscular blocking agents and sedation. All transfer teams carried resuscitation drugs. Only 54% of doctors kept a transfer record. Only 66% of patients transferred had arterial lines, and 33% used end-tidal carbon dioxide monitoring. All patients had ECG monitoring and pulse oximetry. Four of the 24 transfer teams had access to a mobile phone. Pre-transfer laboratory tests were performed in less than 50% of patients. Only 11 of the 24 doctors aimed for a Pa_{O_2} of >13 kPa while 12 of 24 aimed for a Pa_{CO_2} of 4–4.5 kPa. Only four had not heard of the recommendations.

Eight doctors performing neurosurgical transfers did not fulfill the recommendations of having spent at least 2 yr in anaesthesia. Not all patients had invasive arterial monitoring and a substantial number did not have E'_{CO_2} monitoring. More doctors need access to mobile phones. Of concern is the low proportion of doctors who aimed for appropriate Pa_{O_2} and Pa_{CO_2} values. Many transfers fell short of the recommendations. This study will help organize regional education and training, as suggested in the recommendations.

Keywords: intensive care, audit; complications, neurological

References

1. *Recommendations for the Transfer of Patients with Acute Head Injuries to Neurosurgical Units.* The Neuroanaesthesia Society of Great Britain and Ireland and The Association of Anaesthetists of Great Britain and Ireland, 1996.

Why is there increased demand for critical care?

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Critical care services are becoming busier. However, it is not clear from where this expressed demand is generated The aim of this study was to compare changes in hospital activity with those of the hospital's critical care facilities.

The activity (number of beds, hospital admissions, outpatients, inpatient operations and accident and emergency department (A&E) attendances) of three district general hospitals in East Anglia was recorded over 5 yr (1992–1996 inclusive). Trends in these values were compared with activity measures of the critical care services (number of admissions, numbers of bed days provided) and simple patient details (age of patients, type of admission).

The results suggested that while the number of hospital beds has remained static, the activity within the hospitals has increased over the 5 yr (hospital admissions increased by 5%, 8% and 19%, outpatients increased by 12%, 17% and 27%, inpatient operations either

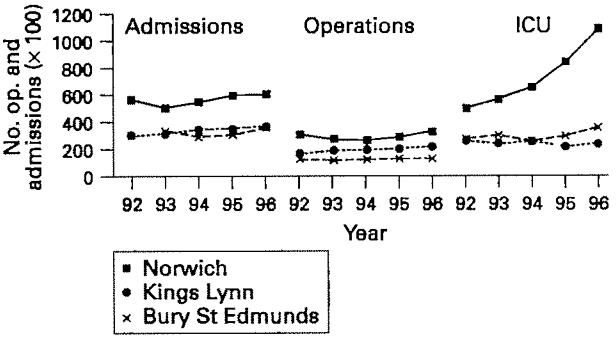

Figure 1 Activity of three district general hospitals in East Anglia over a 5-yr period.

did not change or increased by 4% and 27%, A&E attendances either decreased by 3%, did not change or increased by 17%) (fig. 1). However, the increase in activity was greater for the critical care services. The number of admissions increased by 33% and 119%. In a four-bed ICU, a single bed closure resulted in only a 6% reduction in admission. The number of bed days provided increased by 30%, 33% and 115%. The average age of the critically ill patients increased consistently from a mean in the mid-fifties in 1992 to high-fifties in 1996.

These preliminary results suggest that the hospitals are treating more patients but that the activity of the critical care services is increasing much faster, suggesting that the demand for critical care may be generated from within the hospitals. If these results are confirmed elsewhere, then planning the size of critical care facilities should reflect practices and specialties available within the hospital concerned rather than population demographics.

Keywords: intensive care, audit

Prognostic indices following emergency aortic aneurysm repair

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Emergency aortic aneurysm repair is associated with a high mortality. The aim of this study was to identify important indices which are associated with a poor outcome so that these may be used to augment clinical management.

In this retrospective study, patients who had undergone emergency abdominal aortic aneurysm repair between January 1, 1995 and October 31, 1997 were identified from the theatre and intensive care unit (ICU) records. Previous studies have alluded to a higher mortality in patients who were hypotensive or undergoing cardiopulmonary resuscitation (CPR)[1] and who were elderly.[2] Therefore, the patients' notes were examined for these and other key features which may affect outcome (age, sex, co-morbidity, usual medication, time to surgery, arterial pressure on admission, preoperative CPR, time of surgery (day or night), aneurysm rupture, intraoperative hypotension >20 min (defined as systolic arterial pressure <90 mm Hg), blood loss (litre), seniority of anaesthetist and surgeon, and intraoperative use of inotropes). Univariate analysis was initially used to examine which factors distinguished patients who died from those who survived. Binary logistic regression was used to model those factors which independently and significantly influenced if the patient died in theatre, in the ICU or within 28 days of surgery.

One hundred and thirty-five patients underwent emergency aortic aneurysm repair. Ten medical records could not be traced and therefore 125 patients were included in the study. Univariate analysis revealed that sex, usual medication, time to surgery, time of surgery (day or night), seniority of anaesthetist and surgeon, and intraoperative use of inotropes did not influence outcome at any time. The results of the binary logistic regression are shown in table 7 and the size of the coefficients reflect the relative importance of the prognostic factor.

The results suggested that aneurysm rupture followed by blood loss were the two most important factors in determining outcome from surgery, ICU and short-term survival. These preliminary results indicate that it is possible to identify factors associated with an adverse outcome and such factors could be used to augment clinical judgement.

Keywords: intensive care, audit; surgery, abdominal

References

1. Farooq MM, Frieschlag JA, Seabrook GR, Moon MR, Aprahamian C, Towne JB. *Surgery* 1996; 119: 9–14.
2. Berridge DC, Chamberlain J, Guy AJ, Lambert D. *British Journal of Surgery* 1995; 82: 906–910.

Validation of outcome prediction in elderly patients

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We recently described an equation for predicting 1-yr survival of elderly critically ill patients[1]. The aim of this study was to check the accuracy and discrimination of this equation in a validation group of critically ill patients in the same institution.

Patient details (age, sex, diagnosis, acute physiology score (APS) and number of chronic health evaluation points) and treatment details (planned or unplanned admission, length of intensive care unit (ICU) stay) of all critically ill patients aged more than 70 yr admitted between April 1, 1995 and September 30, 1996, were recorded. Patients were followed for 1 yr by examining the hospital's administrative system; if a date of death could not be found, the patient's general practitioner was asked to provide a date of death or confirm survival. Predicted 1-yr survival was estimated using the equation (as described by Djaiani and Ridley[1]):

Logit $P=0.32+(\text{APS}\times0.07)+(1.52$ if aged $>85)-(\text{diagnosis coefficient})$.

The accuracy of the prediction was checked using the Hosmer–Lemeshow C statistic (measuring goodness of fit) and the discriminatory power by the area under the receiver operating characteristic (ROC) curve.

Of the 555 patients aged more than 70 yr admitted during the study period, 106 died in the ICU (19% ICU mortality, identical to that of the development group[1]) and another 134 died within 1 yr (43% total 1-yr mortality *vs* 47% total 1-yr mortality in the development group). The 1-yr survival of patients aged less than 85 yr was 59% (*vs* 56% in the development group) while that in those more than 85 yr was poor (43% *vs* 27% in the development group; $P>0.05$). The goodness of fit P value was 0.04 (C statistic=19.8, df=10) and the area under the ROC curve was 0.75. However, there were significant differences in the patient details; more patients were admitted electively (40% *vs* 32.2%) and fewer patients with trauma and emergency abdominal aortic aneurysm repair were treated in the validation set. In both groups, the combined 1-yr survival of all critically ill elderly patients was 55% but the outcome of patients aged more than 85 yr remained poor (37%).

Ideally the goodness of fit P value should exceed 0.05, suggesting that the development and validation groups come from the same population. However, our results indicated that this was not the case; the largest difference was the lower than expected number of deaths in the eighth decile risk (spanning 62–71% predicted risk of mortality) in the validation group. The area under the ROC curve failed to reach the accepted standard for discriminatory power (0.8).

Changing patient populations, such as increased elective work and altered diagnoses, may reduce the performance of predictive equations and highlights the difficulty of long-term studies on fluctuating populations of critically ill patients. Revision of the predictive equation is necessary.

Keywords: intensive care, audit; age factors

References

1. Djaiani G, Ridley S. *Anaesthesia* 1997; 52: 1130–1136.

Table 7 Binary logistic regression analysis of factors which independently influenced if the patient died in theatre, in the ICU or within 28 days of surgery

Death	Mortality (cumulative %)	Significant prognostic factors (with coefficients)
Theatre	31.4	Preoperative CPR (–2.75), rupture (–1.78), hypotension (–1.35)
ICU	63.6	Rupture (–1.93), blood loss (–0.278)
Within 28 days	70.2	Rupture (–1.67), blood loss (–0.31), age (–0.064)

How different are critically ill medical patients in the ICU?

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The majority of patients admitted to critical care facilities are surgical and most of the reports concerning critical care are based on cohorts of predominantly surgical patients. There are relatively few reports of non-coronary medical patients in general intensive care units (ICU). The statistical inferences based on surgically based populations may not be valid for medical patients. Therefore, the aim of this study was to examine simple patient characteristics which may distinguish medical from other patients admitted to the ICU.

Patient details (age, sex, diagnosis, acute physiology and chronic health evaluation (APACHE II) score, lead time bias (difference between time of admission to hospital and admission to ICU), admission type (planned or unplanned), length of ICU stay) of all critically ill patients admitted between August 1, 1995 and September 30, 1996 were recorded.

Of the 2165 patients admitted during the study period, 374 (17%) were referred from medical specialties. These patients differed from other critically ill patients in a number of important aspects: (i) the medical patients were younger (mean age 52.6 yr (95% confidence interval (CI) 50.6–54.6 yr)) than the other patients (61.8 (95% CI 60.8–62.7) yr); (ii) APACHE II scores in the medical patients were higher (median 17 (95% CI 1–18)) than those in the other patients (10 (95% CI 10–10)); (iii) ICU mortality of the medical patients was higher (29.1%) than that of the other patients (10.5%), even when corrected for severity of illness; (iv) the lead time bias of medical patients was shorter (median 0.9 (95% CI 0.85–0.94) days) than for other patients (1.7 (95% CI: 1.6–1.7) days); (v) significantly more women were admitted as medical (45%) as opposed to surgical (38%) patients; (vii) 47% of other admissions were planned compared with only 2% of medical patients; and (viii) length of ICU stay did not differ between medical (1.4 days) and surgical (1.0 day) patients.

There are clear patient differences which distinguish medical from other patients. The reasons for such differences are not clear from this study but may relate to either a higher prevalence of chronic co-morbidities or the pan-system nature of acute severe medical disease. The results suggest that medical patients are referred promptly to the ICU but that they suffer a higher than expected mortality when corrected for physiological disturbance. While general scoring systems, such as the APACHE system, cannot be expected to work well in discrete clinical sub groups, medical patients represent a reasonably sized minority in the ICU and so deserve closer attention. Using severity of illness or organ failure scores in medical patients may be unwise and this study suggests that the chances of mortality in such patients may be worst than expected.

In summary, there were significant differences between medical and other patients in the ICU which suggests that general scoring systems should be applied with caution.

Keywords: intensive care, audit

Does transferring patients between hospitals for intensive care alter outcome?

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The question posed by us was whether transferring patients between hospitals for non-clinical reasons for intensive care had a significant effect on ultimate outcome. In the West Midlands, transfers between hospitals for intensive care usually occurred between the 27 local units. This initial study is presented.

The 27 units of the WMICG joined the Intensive Care National Audit and Research Centre (ICNARC) Case Mix programme as a single wave in April 1996. We interrogated the national database using the data available at ICNARC from the West Midlands. Using the 6552 records, a standard query was constructed. Four units were excluded: two specialist paediatric units, an HDU and a regional neuroscience unit because they routinely receive transfers. Planned patients were excluded; 535 unplanned patients were transferred to another hospital for intensive care and were compared with the 4400 unplanned admissions not transferred. Table 8 includes some of the comparisons made.

Table 8 Patient characteristics and hospital details for patients transferred between hospital compared with those not transferred

	Transfers	Non-transfers
Mean age	54.3	56.4
No. female patients (%)	41.9	41.6
No. with past medical history likely to affect outcome present (%)	14.4	14 3
Mean APACHE II score	17.5	17.7
Median APACHE II probability	0.24	0.25
No. of patients ventilated on admission (%)	75.3	59.4
No. of patients receiving CPR before admission (%)	16.3	13.7
Median length of stay in ICU (days)	2.7	1.8
Median length of stay in hospital (days)	12.0	13.0
ICU mortality (%)	26.9	27 0
Hospital mortality (%)	37.8	40.0

The results showed that the two groups of patients were comparable in age and sex distribution, presence of past medical history and severity of illness. There was a small difference in length of stay. The ultimate outcome (mortality) was unaffected by transfer in this sample. We are extending this study to include a larger sample. This would allow incorporation of standardized mortality ratios (SMR) and analysis of more detailed clinical groupings.

Acknowledgement

We acknowledge the analysis of the West Midlands Case Mix data by ICNARC.

Keywords: intensive care, audit; complications, mortality

Sexual dysfunction after intensive care

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Assessment of a patient's quality of life following admission to an intensive care unit (ICU) is becoming increasingly important in auditing intensive care. Many patients report problems that appear to be minor in relation to the severity of their admission diagnosis but which, nonetheless, restrict their current lifestyle and prevent a full return to their pre-admission state of health. We have identified sexual dysfunction as a previously unrecognized complication of admission to the ICU.

We performed a retrospective review of notes of patients who attended the ICU follow-up clinic at 2, 6 and 12 months after discharge from the ICU. Only those whose ICU length of stay was 5 days or more were invited to attend the clinic. Questions covering all aspects of their current state of health and social activities (hobbies, socializing, sex life) were asked, and comparisons made between now and before hospital admission. An assessment of their mental health was made, examining evidence of post-traumatic stress disorder (PTSD). If there was evidence of sexual dysfunction we then considered whether there might be a link with PTSD.

Of the 62 sets of notes reviewed, 16 patients (25.8%) reported sexual dysfunction at 2 months, 12 (19.4%) at 6 months and 10 (16.1%) at 12 months. Of these 10 patients with continuing difficulty (seven male, three female), two were referred to the andrology clinic, one was referred for counselling, two were improving and the remaining five declined further help. Twenty-one patients described symptoms of PTSD, and one-third of these had sexual dysfunction. Of the remaining 41 patients with no evidence of PTSD, 22% had problems sexually.

Sexual dysfunction is a common problem after ICU admission and may often go unrecognized and untreated, despite its major impact on a patient's quality of life. Sexuality after critical illness has not received much attention in the medical literature although patients consider it to be very important.[1] Doctors must be more aware of the problem so that it may be identified and patients' concerns dealt with. We did not find a correlation between PTSD and sexual dysfunction, in contrast with others who have investigated PTSD from other causes.[2]

Keywords: intensive care, audit; complications, sexual dysfunction

References

1. Bunzel B, Wollenek G, Grundbock A, Schramek P. *Herz* 1994; 19: 294–302.
2. De Rios MD, Novac A, Achauer BH. *Journal of Burn Care and Rehabilitation* 1997; 18: 37–42.

Analysis of outcome of ICU patients with acute renal failure in the UK

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We present the salient patient characteristics and prognostic factors that affect outcome from acute renal failure in 21 intensive care units (ICU) in the UK.

Daily APACHE II and TISS data were collected prospectively from 21 ICU between June 10, 1989 and September 14, 1996 until death or discharge. A total of 2395 patients met the following criteria as having acute renal failure: urine output=0 ml/24 h (or <479 ml/24 h and (urea>35 mmol litre^{-1} or creatinine >318 μmol litre^{-1})) or clinical override.[1]

Mean age was 59.7 yr of whom 65.5% were males; 1394 patients were admitted to the ICU, with the above criteria of acute renal failure, and had a mortality of 53% (SMR 1.39); 1001 developed renal failure during their ICU stay, with a mortality of 61% (SMR 2.11).

Mortality for broad admission categories were: emergency surgery (62%); sepsis (69%); haemorrhage (62%); trauma (35%); and elective surgery (33%). Mortality associated with pre-existing co-morbidities were: liver failure (87%); cardiovascular failure (68%); respiratory failure (61%); and immune deficiency (75%). The mortality from acute renal failure alone was approximately 20% and increased to more than 80% when associated with other systems failure (table 9).

The mortality associated with acute renal failure in ICU remains high although the mean age of patients has risen. The SMR for those developing renal failure while in the ICU was higher than that for those admitted with acute renal failure–the risk of the latter being underestimated. This observation, together with the wide range of mortality seen for different subgroups, means that any study evaluating treatment modalities for acute renal failure in the ICU must account for these major confounding factors. Simple randomization alone will not suffice.

Table 9 Mortality from acute renal failure alone and in combination with other systems failure (24% of all deaths occurred in patients with a plasma creatinine concentration of <250 μmol litre^{-1})

Organs	Duration (days)	*n*	Mortality
1	1	381	18%
	2	97	25%
	≥3	62	21%
2	1	531	44%
	≥2	169	53%
≥3	1	651	76%
	2	171	81%
	≥3	164	85%

Keywords: intensive care, audit; kidney, failure

References

1. Knaus W, Draper E, Wagner D, Zimmerman J. *Annals of Surgery* 1985; 202: 685–693.

Increased cerebral venous oxyhaemoglobin saturation and poor outcome in acute brain injury

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Minute by minute, multimodality monitoring of physiological variables in patients with acute brain injury is standard practice in our intensive care unit.[1] This includes arterial pressure, pulse oximetry, temperature, cerebral venous oxyhaemoglobin saturation (Sj_{O_2}), intracranial pressure (ICP) and calculated cerebral perfusion pressure (CPP). Our aim was to analyse Sj_{O_2} and outcome data thus collected, and compare those with a good outcome (Glasgow outcome score (GOS 4 and 5)) with those with a poor outcome (GOS 1–3).

Sixty-two patients with acute brain injury admitted to the ITU had multimodality monitoring as part of their standard care. This included Sj_{O_2} monitoring from the time of admission until it was no longer indicated. An Oximetrix 3 system was used for 58 patients and an Edslab dual lumen oximetry catheter[2] for four. Each physiological variable was considered individually for each patient. In order to make comparisons between patients, time spent outwith normal physiological values (insult time) was expressed as a percentage of validated monitoring time for that variable for each patient. Fifty-four percent of data collected by the Oximetrix 3 system was valid. Patients were assessed at 12 months after injury using the Glasgow outcome score.

Sixty-two patients (51 males), 36 GOS 1–3, 26 GOS 4 and 5, aged 12–70 (mean 37) yr, admitted for intensive care following severe (GCS <8, n=48) or moderate (GCS 8–12, n=14) acute brain injury were studied. GCS after resuscitation was 3–12 (median 7) and injury severity scores (ISS) 13–41 (median 21). Considering the types of brain injury (some patients may have more than one) 12 patients had an epidural haemorrhage, 28 an acute subdural haematoma, five a chronic subdural haematoma, 30 with contusions, 15 diffuse brain injury and four a depressed skull fracture. There was no significant difference between the good (GOS 4 and 5) and poor (GOS 1–3) outcome patient groups for any of the above variables. Poor outcome patients spent significantly more time (as a percentage of monitored time) with an Sj_{O_2} value greater than 75% (P=0.018, normal values 54–75%), ICP >20 mm Hg (P=0.048) and CPP less than 60 mm Hg (P=0.041).

We have confirmed the findings in previous studies of poor outcome associated with increased ICP, and low CPP; however the association between high Sj_{O_2} and GOS has not been demonstrated previously. An increased Sj_{O_2} may be associated with either brain hyperaemia or failure to use oxygen; the injured brain produces inflammatory mediators, and indeed a systemic inflammatory response may ensue following such an injury. We believe the severely injured brain fails to use oxygen appropriately, and hence an increased Sj_{O_2} is seen in patients who have a poor outcome. Our standard treatments for acute brain injury management are aimed at reducing or preventing secondary insults, and this may be why we have not shown a difference in outcome when low Sj_{O_2} is considered. In summary, we report a new finding of high Sj_{O_2} associated with poor outcome in patients with acute brain injury.

Keywords: intensive care, audit; oxygen, saturation

References

1. Jones PA, Andrews PJD, Midgley S. *Journal of Neurosurgical Anaesthesiology* 1994; 6: 4–14.
2. Souter MJ, Andrews PJD. *British Journal of Anaesthesia* 1996; 76: 744–746.

Complications in the first 48 h after surgery: comparison between the general ward and HDU

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Not every hospital has a high dependency unit (HDU). Most acute hospitals, however, have intensive care units (ICU) containing approximately one bed for every 100 general ward beds.[1] In practice, because of the increasing demand for ICU beds, only patients requiring assisted ventilation and invasive cardiovascular monitoring are admitted. As a result of changes in the NHS, there is a deficiency of care for patients who need constant observation but are not considered sufficiently ill to justify transfer to an ICU. Evidence demonstrating a reduction in postoperative complications by admitting patients to an HDU instead of the general ward is lacking. Therefore, this study was undertaken to find the incidence of postoperative complications occurring in the first 48 h after major surgery and to explore the role of the HDU in postoperative care.

The POSSUM (*P*hysiological and *O*perative *S*everity *S*core for the en*U*meration of *M*ortality and morbidity) scoring system was adopted to assess patients.[2] Complications were assessed by clinical observation, interviews with nursing staff and patients, and referral to fluid and drug charts. Data were collected for 426 patients.

The POSSUM score for patients admitted to the HDU was higher than for patients admitted to the general wards (30.8 *vs* 37.4; *P*<0.001). There were similar complications per 10 POSSUM points in HDU patients (median complication per 10 points for HDU patients 0.86 *vs* 0.87 for ward patients). We used analysis of covariance to hold the effect of POSSUM score constant while testing for a difference in the number of complications between the general ward and HDU. The number of complications significantly varied with POSSUM score and not the location of the patient. Four patients admitted to the general wards were admitted within 48 h to the ICU. None from the HDU required ICU admission. There were two deaths in the general ward and two in the HDU.

The higher complication scores for HDU patients were a result of the higher POSSUM score and perhaps also to closer nursing observations. Although it has been shown that the number of complications was not significantly different between the HDU and the ward, the quality of care may be better in the HDU in terms of mortality and deterioration requiring subsequent ICU admission.

Keywords: intensive care; complications

References

1. Rhodes A, Lamb FJ, Grounds RM, Bennett ED. *British Journal of Intensive Care* 1997, 7: 237–243.
2. Copeland GP, Jones D, Walters M. *British Journal of Surgery* 1991; 78: 355–360.

Are deaths on hospital wards potentially preventable?

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Comparing admissions to the intensive care unit (ICU) from the operating theatres/recovery, the accident and emergency department (A&E), and the wards, the largest number and highest percentage of deaths are in patients admitted from the wards.[1] Deaths of some patients who die on the ward may be preventable by early identification and ICU admission. A prospective study of all ward deaths was undertaken to quantify this problem.

The notes of all patients who died on the wards between June 1 and November 30, 1997 were examined. If a "do not resuscitate" (DNR) order was in the notes, the time of the order before death was recorded. For patients without DNR orders, information was collected on physiological values, procedures and interventions in the 24 h before death.

During the study period, 316 patients died on the wards, excluding deaths in the ICU, A&E, coronary care and the radiology department. A DNR order was in the notes of 261 (83%) patients. During their hospital admission, 14 (5.4%) of those with DNR orders had been in the ICU and 13 (5%) had received cardiopulmonary resuscitation (CPR). In 11, the date of the DNR order was uncertain. The remaining 250 patients had a mean age of 74.9 yr (range 34–96 yr) and were in hospital a median of 11 (range 0–204) days before death. DNR orders were recorded a median of 3.2 (0–131) days before death. For 17% the DNR order was on the day of death and in 35% it was within 1 day of death.

A DNR order was not made for 55 patients (17%). However, from the diagnoses, resuscitation was not always appropriate. Four (7%) had a previous ICU admission and 17 (31%) received CPR before death. Mean age was 66.1 yr (range 21–90 yr) and median hospital stay before death was 8 (range 0–83) days. Routine physiological values were often recorded for the 24 h before death (table 10). Missing values were assumed to be normal, resulting in an average APACHE II score of 13.3 (SD 6.0).

Many patients who died on the wards were in hospital for some days before death. A high percentage of DNR orders were made shortly before death, suggesting that active treatment was pointless at this time. However, earlier intervention may have been of benefit in some patients Some patients without a DNR order were not appropriate for CPR. Earlier identification, active management and ICU admission may have been of benefit in others.

Keywords: intensive care, audit; complications, mortality

References

1. Goldhill DR, Sumner A. *Critical Care Medicine* 1998, in press.

Table 10 Percentage physiological values recorded and average APACHE II points. Temp=temperature, MAP=mean arterial pressure, HR=heart rate, Resp=respiratory frequency, Oxy=oxygenation score, Na=sodium, K=potassium, Creat=creatinine, Hb=haemoglobin, WBC=white cell count, GCS=Glasgow coma score, %=percentage for whom a value was available in the 24 h before death. Avg points=average APACHE II points in the 24 h before death

	Temp	MAP	HR	Resp	Oxy	pH	Na	K	Creat	Hb	WBC	GCS
%	84	76	89	64	15	16	67	65	65	60	60	7
Avg points	1.0	1.5	1.8	1.2	0.9	1.9	0.2	0.3	2.2	0.7	0.8	9.3

APACHE II, data accuracy and outcome prediction

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The precise way in which APACHE II scoring is applied often differs from the way it was developed originally. Potential errors in scoring and their impact on prediction need to be studied [1] In our ICU, APACHE II data are collected prospectively using a standard form and definitions. A chart review was undertaken to identify potential errors in these data.

Every 10th ICU admission chart in 1995 and 1996 was examined. Patients who underwent cardiac surgery, those less than 17 yr, those who died or were discharged within 8 h of admission or those with a previous admission were excluded. The charted data were assumed to be accurate and the highest and lowest charted values in the 24 h after admission were recorded for eight physiological variables (table 11). pH, sodium, potassium and haemoglobin values measured in the ICU laboratory were the values taken from the chart. Sodium, potassium and haemoglobin values were also measured daily in the hospital laboratory. APACHE II points were calculated and compared with values in the ICU database Predicted hospital mortality and mortality ratio (MR) (observed hospital deaths/predicted deaths) were also calculated.

A total of 122 charts were eligible for comparison. If the chart review values are assumed to be accurate, an average of 1 73 more APACHE II points were scored. Predicted mortality increased from 24.8% to 27.8%. MR (95% confidence interval) decreased from 1.52 (1.11–2.03) to 1.35 (0.99–1.81). Inaccuracy and inconsistency in data collection must be excluded before differences in mortality ratios are ascribed to ICU performance

Keywords: intensive care, audit; complications, mortality

Reference

1. Rowan K. *Current Opinion in Critical Care* 1996; 2: 209–213.

Table 11 Charted data compared with ICU database for eight physiological variables. Percentage higher and lower compares chart review with ICU database; the kappa statistic describes the inter-observer difference between the ICU database and chart review

	ICU database	Charts			
Variable	Average points	Average points	% higher	% lower	kappa
Temperature	0.61	0.54	5.7	9.8	0.72
Mean arterial pressure	0.92	1.04	16.4	9.8	0 53
Heart rate	1.19	1.70	28.7	5.7	0.45
Respiratory rate	0.40	0.36	14.8	8.2	0.42
pH	0.92	1.19	27.9	5.7	0.51
Sodium	0.34	0.57	13.1	0.8	0.65
Potassium	0 39	0.69	32.0	6.6	0.34
Haemoglobin	0.64	1.07	26.2	6.6	0.39
All 8 variables	5.42	7.15	20.6	6.7	

The patient at risk team: identifying and managing critically ill ward patients

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Ward patients have abnormal physiological values associated with ICU admission and cardiopulmonary resuscitation (CPR).[1] Based on this work a patient at risk team (PART) was developed to assess ward patients who had a combination of physiological abnormalities. A doctor or senior ward nurse could also call the PART for a patient causing concern. The main criteria for alerting the PART were a patient with any 3 **or more** of the following: respiratory frequency ≥25 bpm (or <10 bpm); not *fully* alert and orientated; systolic arterial pressure <90 mm Hg; oxygen saturation <90%; heart rate ≥110 beat min^{-1} (or <55 beat min^{-1}); urine output <100 ml over the last 4 h; **or** the patient not fully alert **and** orientated and respiratory frequency ≥35 bpm **or** heart rate ≥140 beat min^{-1}

The PART was introduced on the June 1, 1997. In the first 6 months the PART was called 69 times to 63 patients. A decision was taken to admit the patient immediately to the ICU, to review and admit later if necessary, not to review or that ICU admission was inappropriate; 38 (60%) were admitted to the ICU at sometime after assessment.

There were 27 assessments in 27 patients resulting in ICU admission within 48 h. Nine of these patients died. Of the other 42 assessments in 36 patients, two patients were considered to be inappropriate for ICU admission. Eleven patients were later admitted to the ICU; three (who all died) within 48 h of a further assessment, and the others, 3–33 days after being seen. There were three deaths in patients admitted to the ICU more than 48 h after being seen and four deaths in patients who were not admitted to the ICU. In total, 19 patients died (32%) and all but four were admitted to the ICU sometime after being seen by the PART.

Eight (27%) of those admitted within 48 h of assessment fulfilled the main criteria above for calling the PART compared with 13 (33%) of those not admitted within 48 h. When assessed, the commonest physiological abnormality was a respiratory rate >25 bpm, found in 63% of those admitted within 48 h and in 49% of the others. The next commonest abnormalities were being not fully alert and orientated, and tachycardia. There was no significant difference between groups in APACHE II scores for the 24 h before being assessed (14.9 admitted <48 h, 12.8 not admitted).

Most patients assessed did not fulfil the main physiological criteria for calling the PART and these criteria need to be refined. Neither the physiological criteria nor APACHE II scores identified patients who were admitted to the ICU within 48 h, although ICU admission may have been affected by bed availability. Awareness of potential ICU patients on the wards allowed us to suggest changes in management, and to plan ICU admissions.

Keywords: intensive care, audit; complications, mortality

Reference

1. Goldhill DR, White SA, Brohi K, Sumner A. *Clinical Intensive Care* 1997; 8: 103.

Patients admitted to the ICU from the ward: effect of the patient at risk team

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Comparing ICU admissions from the operating theatres/recovery, the accident and emergency department (A&E), and the wards, the largest number and highest percentage of deaths are in patients admitted from the wards.[1] Deaths may be preventable by early identification and ICU admission of critically ill ward patients. On June 1, 1997, a patient at risk team (PART) was introduced at the Royal London Hospital to assess critically ill ward patients. All patients admitted from the wards to the ICU between June 1 and November 30, 1997 were studied prospectively to assess the effect of the PART.

Patients were grouped by those who had and those who had not been seen by the PART in the 48 h before admission. A record was made of those receiving cardiopulmonary resuscitation (CPR) before admission and APACHE II scores, and predicted hospital outcome was calculated from the worst physiological values in the 24 h after ICU admission

A total of 422 patients were admitted to the ICU, 103 from the wards. Of those admitted from the wards 30 were seen by the PART within 48 h of admission. Significantly fewer patients seen by the PART received CPR (fig. 2). Although predicted hospital mortality was lower for patients seen by the PART, as was ICU mortality, this did not reach statistical significance. For patients not seen by the PART, predicted mortality and APACHE II scores

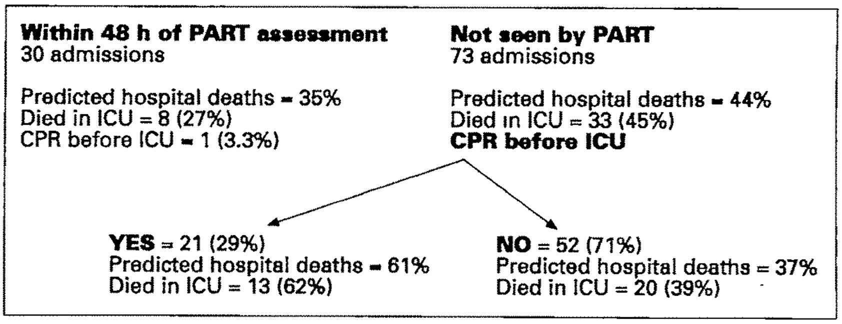

Figure 2 Admissions to ICU from the ward, June–November 1997.

were significantly higher in those who received CPR, although the difference in ICU mortality was not statistically significant (P=0.59). As several patients had more than one ICU admission but can only die once, we have shown only ICU mortality.

A high percentage of ICU admissions are from the wards where patients are available for early intervention. We relied on ward staff to call the PART. Whether this was done may have depended on ward practice and combinations of abnormal physiology and pathology. If those assessed and those not assessed by the PART are comparable, the PART appears to significantly decrease the incidence of CPR and may also decrease mortality. If the need for CPR can be prevented, lives can almost certainly be saved.

Keywords: intensive care, audit; complications, mortality

Reference

1. Goldhill DR, Sumner A. *Critical Care Medicine* 1998; in press.

A multi-centre study of obstetric admissions to intensive care units in Southern England

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The *Confidential Enquiry into Maternal Deaths*[1] provides valuable mortality statistics, however less is known about life threatening complications of pregnancy and childbirth and the requirement of this population for admission to the intensive care units (ICU).[2]

Data in the ICU admissions between April 1, 1994 and December 31, 1996 were analysed retrospectively to identify patients admitted either because of complications of pregnancy or with concurrent medical conditions whose status was adversely affected by parturient state. Data were verified by personal visits to the hospitals involved. For all patients, obstetric details, patient characteristics, severity of illness data and therapeutic interventions were recorded. Predicted risks of hospital mortality were derived for each patient using three systems; APACHE II, III and SAPS II. Standardized mortality ratios (SMR) were used to compare observed and predicted hospital outcome. The goodness of fit of the three scoring systems was assessed using receiver operator characteristic (ROC) curve analyses

A total of 11 359 patients were admitted to 14 ICU in the study period: 210 obstetric patients were identified, representing 1.01% (median 0.89% (range 0.18–3.18%)) of all ICU admissions and 0.17% (0.04–0.6%) of total deliveries in the obstetric units concerned. Median age was 30 (16–45) yr and the median length of stay (LOS) in the ICU was 1 (1–34) days. Therapeutic interventions are shown in table 12. A total of 205 (97 6%) patients had severity of illness data available. Table 12 also shows the observed and predicted hospital death rates, SMR and areas under the ROC curve for each of the three severity of illness scoring systems.

Admissions to ICU during pregnancy and childbirth are infrequent, often require minimal intervention and have low mortality, with wide variation between ICU. The SMR suggest good ICU performance and the ROC data indicate reasonable goodness of fit but the small overall numbers limit full statistical inference.

Table 12 Therapeutic interventions in obstetric patients admitted to the ICU during the study period and observed and predicted hospital death rates, SMR (with 95% confidence intervals) and areas under the ROC curve for each of the three severity of illness scoring systems (AII=APACHE II, AIII=APACHE III). *ICU LOS ≤2 days; †six patients died in the study group

	Interventions % (n)	Interventions (Range %)
IPPV	45 (95)	0–78
Inotropes	19 (40)	0–60
PAC	13 (28)	0–32
CVVH	3 (7)	0–14
None of above*	35 (75)	0–60

	Predicted deaths (n)†	SMR [95% CI]	Area under ROC
AIII	13.8	0.43 [0.16–0.95]	0.98
AII	25.4	0.24 [0.09–0.52]	0.94
SAPS II	14.1	0.43 [0.15–0.93]	0.90

Keywords: intensive care, audit; intensive care, obstetric

References

1. *Confidential Enquiry into Maternal Deaths 1991–93.* London: HMSO.
2. Harmer M. *Anaesthesia* 1997; 52: 99–100.

Evaluation of predicted and actual length of stay in 22 Scottish ITU using the acute physiology and chronic health evaluation III (APACHE III) system

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The acute physiology and chronic health evaluation (APACHE) prognostic system has grown from data in a single intensive care unit (ICU) in 1979 to a system that has collected information on more than 300 000 admissions worldwide.[1] Initially, the APACHE system was used to predict mortality, but the APACHE III system has been developed to predict length of stay in the ICU, in both the critically ill and after coronary artery bypass grafting.[2]

In a multi-centre, national cohort study involving 22 adult ICU in Scotland, we studied data on 10 327 consecutive patients Our results showed that on an individual basis, there was a poor correlation between predicted length of stay and that actually observed.

Regression analysis showed an r^2 value of 0.113. This was further broken down into ICU deaths and ICU survivors. Correlation for survivors was similar (r^2=0.141), but that for ICU deaths was much worse (r^2=0.032). When data were grouped together as predicted length of stay (days) and plotted against actual stay, there was a consistent over prediction of the time actually spent in the ICU. This was even more apparent in the deaths in the ICU group

On a centre by centre basis the average ratio of actual:predicted length of stay in the ICU was 0.76. These length of stay ratios varied from 0.55 to 1.16. The correlation of these units resulted in an r^2 value of 0.43. This was compared with US data which showed a mean length of stay ratio of 0.88–1.21, and a correlation coefficient of all units around the line of identity of 0.78.

The ability to predict length of stay would provide a measure of quality of care complimentary to the standardized mortality ratio (SMR). However, the current APACHE III methodology does not achieve this for the Scottish population.

Keywords: intensive care, audit

References

1. Knaus WA, Wagner DP, Zimmerman JE. *Chest* 1991; **100**: 1619–1636.
2. Knaus WA, Wagner DP, Zimmerman JE, Draper EA. *Annals of Internal Medicine* 1993, **118**: 753–760.

Prognosis of patients admitted to the intensive care with life threatening medical complications of haematological malignancy: has it changed?

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In the 1980s, we and others documented the poor prognosis of patients receiving intensive care for life threatening medical complications of haematological malignancy.[1] More recent studies have shown that the prognosis is even worse for patients admitted to intensive care after bone marrow transplantation, especially when they require mechanical ventilation.[2] We wondered if changes in admission policy, supportive treatment (e.g. more frequent use of mask CPAP, introduction of pressure limited ventilation) and the altered patient population had been associated with a change in prognosis.

The case notes of all patients admitted to the intensive care unit (ICU) with life threatening medical complications of haematological malignancy over a 5-yr period from January 1991 to December

1996 were reviewed retrospectively. The underlying diagnosis, nature of the acute illness and treatment received were noted. Severity of illness was assessed using the admission APACHE II score. Factors significantly associated with in-hospital mortality were identified using chi-square or, where appropriate, Fisher's exact test. $P<0.05$ was considered to be significant.

Forty-eight patients (26 females) with life threatening medical complications of haematological malignancy were admitted to the ICU during this 5-yr period. Median APACHE II score was 22 (range 6–35). Hospital mortality in the 19 patients who had received a bone marrow transplant (BMT) was 95% whereas 24% of the remaining 29 patients survived to leave hospital. There were no survivors among patients with a diagnosis of chest infection associated with sepsis ($n=11$), four or more organ failures ($n=7$), or among those who had undergone pulmonary artery catheterization ($n=21$), haemofiltration ($n=3$) or pressure control ventilation ($n=12$). No patient who received norepinephrine ($n=18$) or dobutamine ($n=9$) survived. Pulmonary artery catheterization, mechanical ventilation and administration of norepinephrine were significantly associated with death in hospital ($P<0.01$, $P=0.03$ and $P=0.02$, respectively). Among patients who had undergone BMT there were no survivors with a diagnosis of chest infection ($n=15$), isolated respiratory failure ($n=17$) or an APACHE II score >20. No BMT patient who received mechanical ventilation ($n=13$) or an epinephrine infusion ($n=7$) survived.

These observations suggest that the outcome of intensive care for patients with life threatening medical complications of haematological malignancy who have not received a BMT has not changed significantly since the mid-1980s. Our findings also confirm that the prognosis for those patients who have undergone BMT is particularly poor, especially when they are admitted with respiratory failure.

Keywords: intensive care, audit; complications, haematological

References

1. Lloyd-Thomas AR, Wright I, Lister TA, Hinds CJ. *British Medical Journal* 1988; 296. 1025–1029.
2. Crawford SW, Petersen FB. *American Review of Respiratory Diseases* 1992; 145: 510–514.

Peptidoglycan derived from the cell wall of a non-pathogenic gram-positive bacterium synergises with endotoxin to cause organ injury/dysfunction in the rat

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In the majority of septic patients with documented bacterial infection, both gram-positive (G+ve) and gram-negative (G-ve) organisms are isolated. Polymicrobial or mixed infections are associated with a particularly high mortality.[1] We have recently shown that peptidoglycan (PepG) derived from the cell wall of the pathogenic G+ve bacterium *S. Aureus* synergizes with low dose *E. coli* endotoxin (LPS) to cause organ injury–dysfunction in the anaesthetized rat. Here, we have investigated if PepG isolated from the non-pathogenic G+ve bacterium *B. subtilis* also synergises with low dose LPS in the same model.

Male Wistar rats were anaesthetized with thiopental 120 mg kg^{-1} i.p. Animals then received either *E. coli* LPS 0.1 mg kg^{-1}, i.v. ($n=9$), *B. subtilis* PepG 10 mg kg^{-1}, i.v. ($n=7$) or a combination of LPS and PepG in the same doses given together ($n=11$). A control group, ($n=8$) received an equal volume of vehicle (saline). All rats received i.v. saline 6 ml kg^{-1} h^{-1} throughout the experiment. Mean arterial pressure and heart rate were monitored continuously. Blood was collected at 90 min for measurement of tumour necrosis factor-a (TNFa) by ELISA and at 6 h for determination of biochemical indices of organ injury. In contrast with either LPS or PepG alone, the combination produced significant delayed hypotension (data not shown), a larger increase in TNFa concentrations and severe organ injury/dysfunction (table 13).

These findings may help to explain the relatively high mortality associated with polymicrobial and mixed infections, and also the deleterious effects of translocation of bacteria, or their cell wall components, from the gut lumen. They also suggest that administration of bactericidal antibiotics to patients colonized or infected with pathogenic or non-pathogenic G+ve organisms could, in the presence of only small amounts of endotoxin, precipitate shock and organ injury.

Acknowledgement

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Keywords: infection, bacterial; rat

Reference

1. Weinstein MP, Murphy JR, Reller LB, Lichtenstein KA. *Reviews of Infectious Diseases* 1993; 5: 54–70.

Table 13 Values are expressed as mean (SEM). *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with control (ANOVA+Bonferroni's post test)

Group	TNFa (ng ml^{-1})	Creat (µmol litre^{-1})	Bilirubin (µmol litre^{-1})	AST (iu litre^{-1})	ALT (iu litre^{-1})	Lipase (iu litre^{-1})
Control	0.6 (0.2)	31 (3)	2.3 (0.4)	182 (26)	73 (6)	3.3 (2)
LPS (0.1 mg kg^{-1})	14 (4)*	36 (3)	3.5 (0.7)	294 (18)	136 (14)	15 (4)
PepG (10 mg kg^{-1})	12 (2)	32 (7)	4.8 (1)	177 (13)	107 (5)	12 (6)
LPs+PepG	47 (3)***	54 (6)*	16 (3)***	902(222)**	586 (181)**	102 (16)***

Temperature changes in patients undergoing secondary transport

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Patients undergoing secondary transport are usually critically ill, may be sedated, paralysed and undergoing mechanical ventilation. All of these can result in heat loss. The journey outside the hospital and in the ambulance also results in heat loss which may be detrimental as decreases in core temperature are associated with reduced cardiac output, increased systemic vascular resistance and myocardial ischaemia.[1] Previously, with no definite protocol for temperature conservation, we performed an observational study of 12 patients to assess their temperature changes. This was a follow-up study using standardized heat conservation methods, assessing the efficacy of these methods in 20 patients.

This study was conducted in winter. Patients undergoing secondary transport journeys of at least 15 min, who were undergoing mechanical ventilation, sedated or paralysed were included. A nasopharyngeal temperature probe was inserted. Heat conservation included using clear polythene applied to the patient's truncal area adjacent to the skin. Patients were then covered with two blankets. All had a heat and moisture exchanger. The ambulance was heated to a comfortable temperature. Values noted included core and ambient temperatures, journey time, mean ambulance temperatures at start, mid and end-journey.

Mean ambient temperature in the ambulance at the start of the journey was 14.2°C (13.1°C in an earlier study where ambulance was unheated), mid-jouney 15.7 (14.0)°C and at the end of the journey 17 (15)°C. Mean journey time was 26.1 min. Patient temperature changes as a result of the journey were defined as the difference in core temperature on arrival at the receiving unit and core temperature at the referring site (i.e. core 2–core1). Differences in core temperatures (core 2–core1) ranged from +0.4 to –0.3°C. In the earlier study with no standard heat conservation, three of 12 (25%) patients had an increase in (core 2–core 1) of at least +0.1°C, 9 (75%) showed no increase or had a decrease in (core 2–core 1) of at least 0.1°C. In this current study, 10 patients had an increase of at least +0.1°C. Ten of 20 patients (50%) had no increase or showed a decrease in core temperatures of at least 0.1°C.

With attention to heat conservation, the percentage of these at risk patients gaining body heat over the journey period increased from 25 to 50%. These heat conservation methods did not add any significant costs, and will subsequently be our standard practice.

Keywords: temperature, effects

Reference

1. Evans JHW, Singer M, Chapple CR, MacCartney N, Walker JM, Milroy EJG. *British Medical Journal* 1992; 304: 666–671

The auditory evoked response in cerebral malaria

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The auditory evoked response (AER) reflects the function of the auditory pathway and primary auditory cortex. Changes that occur in the AER correlate with depth of anaesthesia and levels of sedation,[1] and have also been used to predict outcome in certain defined conditions requiring intensive care[2] Parallels exist between the coma associated with cerebral malaria and general anaesthesia, in that they both produce loss of consciousness, which in the absence of other complications, reverses rapidly and without sequelae. Similarities in the AER had been noted in a single patient with cerebral malaria at Northwick Park. This pilot study measured the AER in six patients admitted to Gokwe District Hospital, Zimbabwe over a 2-week period with coma secondary to malaria confirmed by blood screening. Each patient had AER recordings for 1–4 days depending on outcome.

The auditory brain stem response was evident in all six patients. In most cases the early cortical complex Pa/Nb/Pc was clearly represented and was similar to the AER we have seen at light levels of anaesthesia. When the patient was in coma, Nb latency increased to greater than 45 ms and on recovery reduced to less than 45 ms (fig. 3). A similar latency change has been shown previously to reflect awakening from anaesthesia.[1] An arousal effect in the AER was also observed (i.e. shortening of Nb latency) when we shouted at the patient, despite the fact that clinically the patient was unresponsive.

In this small study, no correlation was found between depression of the AER and the Glasgow coma score, which suggests that these measurements reflect different aspects of brain pathology.

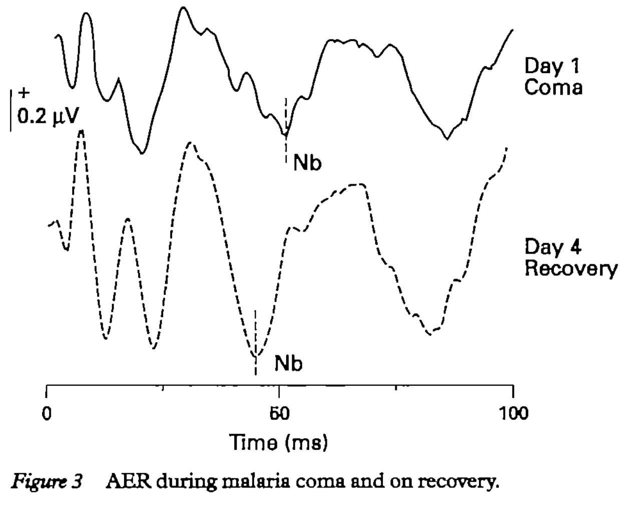

Figure 3 AER during malaria coma and on recovery.

Keywords: brain, evoked potentials; complications, malaria; complications, coma

References

1. Thornton C. *European Journal of Anaesthesiology* 1991; 8: 89–107.
2. Butinar D, Gostisa A. *Pflugers Archiv European Journal of Physiology* 1996; 431 (Suppl. 2): R289–R290.

Procalcitonin and mortality in children with septic shock

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We have documented the relationships between procalcitonin (PCT), C-reactive protein (CRP), leucocyte count (WCC) and mortality in children with septic shock. Also, we wished to establish if persistently increased PCT, despite antibiotic therapy, is an adverse prognostic indicator.

Fifty-one children with septic shock, mortality 16/51 (31%), median age 29 months (interquartile range (IQ) 2–99 months), were enrolled. PCT, CRP and WCC were measured on admission to the paediatric intensive care unit (PICU). Sequential PCT concentrations were measured in 15 children. PCT was measured by immunoluminometric assay (BRAHMS Diagnostika, Berlin, Germany) with reference ranges (ng ml^{-1}) of: uninfected <1, viral infection <2, localized bacterial infection <5, systemic bacteraemia 5–500. Results were analysed by Mann–Whitney and Fisher's exact tests.

Median PCT was 91.6 (IQ 22–323) ng ml^{-1}, median CRP 86 (IQ 29–112) mg litre^{-1} and median WCC 12.9×10^9 litre^{-1} (IQ 5.7–18.1×10^9 litre^{-1}). Admission values for survivors and non-survivors are shown in table 14.

Table 14 Admission values of PCT, CRP and WCC in survivors and non-survivors

	Survivors (n=35) (69%)	Non-survivors (n=16) (31%)	P
PCT	76 (22–236)	314 (84.7–500)	0.01
CRP	101 (43–114)	55 (26–108)	0.28
WCC	14.2 (9.0–19.5)	5.6 (4.2–16.0)	0.05

Failure of the 24-h PCT to decrease to less than the admission concentration was associated with 63% mortality (five of eight patients), in contrast with zero mortality in those seven patients whose PCT decreased with treatment (P=0 025) Persistently increased PCT had a positive predictive value of 63% and a negative predictive value of 100% for mortality.

In summary, we conclude that persistently increased procalcitonin concentrations, despite treatment, is an adverse prognostic indicator in children with septic shock.

Keywords: complications, septic shock; complications, mortality

Microvascular changes in children with meningococcal disease

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Venous occlusion plethysmography (VOP) has previously been used in the non-invasive assessment of microvascular filtration capacity (Kf) and isovolumetric venous pressure (*Pvi*) in humans.[1] Previous studies in healthy children have shown an age dependent variation in Kf. Greater permeability of new microvessels has previously been documented[2] and may be implicated to explain this variation. Our preliminary data have been compared with the appropriate age-matched controls from these studies. We have used VOP to quantify changes in the microcirculation in children with meningococcal disease (MD). MD is associated with a profound capillary leak syndrome, the exact aetiology of which remains unclear.

We used a cumulative congestion pressure step protocol[1] for the assessment of Kf and *P*vi in the calves of subjects. A total of 20 children with MD were studied (nine males; age range 1.25–16 yr). Kf is significantly increased in children with MD (P=0.035) and is highest in children less than 5 yr. *P*vi in these children showed a linear relationship with Kf (fig. 4).

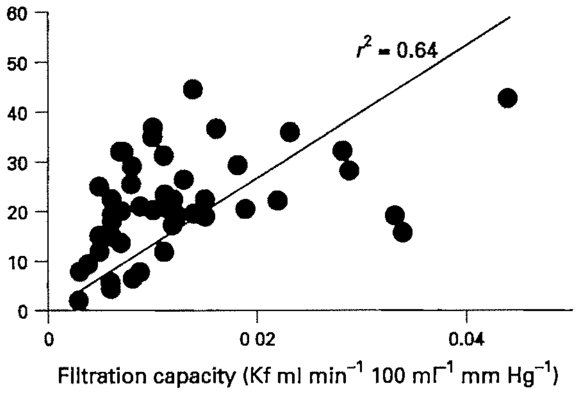

Figure 4 Relationship between Kf and *P*vi in meningococcal disease.

We have demonstrated that VOP can be used to quantify the increased Kf in children with MD.[2] Kf and *P*vi appear linearly related. This is in keeping with passive tilt studies performed in healthy adult volunteers which have demonstrated an increase in *P*vi related to the veno-arteriolar reflex which is activated by passive tilting.[3] We postulate that sepsis (resulting in increased Kf and post-capillary obstruction caused by white cell margination) and passive tilting (secondary to reflex arteriolar vasoconstriction) both cause decreased microvascular flow, reflected in an increase in measured *P*vi. In MD, increased *P*vi may reflect decreased nutritive flow and the risk of subsequent multiple-organ failure.

Keywords: complications, meningococcal disease

References

1. Gamble J, Gartside IB, Christ F. *Journal of Physiology (London)* 1993; **464**: 407–422.
2. Schoeft GI. *Virchows Archives of Pathological Anatomy* 1963; 337. 97–141.
3. Gamble J, Christ F, Gartside IB. *Journal of Physiology (London)* 1997; **498**: 541–552.

Binding of calcium to albumin and gelatin solutions

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Up to 45% of total plasma calcium binds to serum albumin. The ionized fraction of calcium may increase in hypoalbuminaemia. Conversely, giving exogenous albumin may reduce ionized calcium.[1] Gelatin solutions are commonly used as plasma expanders in the critically ill. The extent to which calcium binds to gelatin may differ from albumin. We wished to study the *in vitro* binding of calcium to human albumin solution and a succinylated gelatin solution.

We prepared six concentrations of albumin (Zenalb, BPL, London, UK) and five concentrations of Gelofusine (B Braun Ltd, Aylesbury, UK). We used 0.9% saline as a control solution. To each solution we added varying concentrations of $CaCl_2$. Ionized Ca^{2+} and H^+ concentrations were measured using a Ciba-Corning 288 blood gas system machine.

At all concentrations, ionized Ca^{2+} was the same as the total calcium in the saline solution. The ratio of the measured ionised Ca^{2+} concentrations for the albumin and Gelofusine series of solutions are given in table 15. In all but two comparisons, ionized Ca^{2+} was higher in the albumin solution.

Table 15 Ratio of ionized calcium concentrations for albumin:Gelofusine

Albumin–Gelofusine	$CaCl_2$ concentration (mmol litre^{-1})					
concn (%)	3.0	2.5	2.0	1.5	1.0	0.5
4.0	1.14	1.17	1.20	1.19	1.27	1.38
3.0	1.15	1.14	1.22	1.09	1.17	1.11
2.0	1.23	1.17	1.10	1.12	1.13	1.07
1.0	0.99	1.04	1.03	0.97	1.10	1.10
0.5	1.18	1.15	1.10	1.01	1.22	1.11

These data show that Gelofusine binds calcium to a greater extent than albumin. This may be a function of pH (albumin pH 6.5±0.1; Gelofusine pH 6.68±0.17). Ca^{2+}–albumin binding may be decreased at lower than physiological pH.[2]

Keywords: ions, calcium; fluids i.v.

References

1. Mimouni A, Mimouni F, Mimouni C, Mou S, Ho M. *Pediatric Emergency Care* 1991; 7: 149–151.
2. Kragh-Hansen U, Vorum H. *Clinical Chemistry* 1993; **39**: 202–208.

Clinical associations with bacterial translocation

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Gut translocation of bacteria (BT) may be important in the aetiology of multi-organ failure. Surprisingly little information is available as to the prevalence of this phenomenon in different patient groups. In this study, gut translocation of bacteria was assessed by culture of mesenteric lymph nodes and serosal scrapings taken at laparotomy Standard microbiological techniques were used.

A total of 448 patients were studied. BT to mesenteric lymph nodes was identified in 69 patients (15.4%). Comparison of individual patient groups revealed no significant difference in the incidence of translocation between benign and malignant disease (17% *vs* 13%), inflammatory bowel disease and other GI disease (20 *vs* 15%), significant weight loss and no weight loss (10% *vs* 15%) and total parenteral and enteral feeding (18% *vs* 14%). However, translocation was more common in patients with intestinal obstruction (30%) than in those without obstruction (13%, $P<0.01$). The more distal the level of obstruction, the greater the incidence of translocation Postoperative septic complications were more common in patients with confirmed BT ($P<0.001$).

We conclude that the incidence of BT is highest in patients with intestinal obstruction.

Keywords: infection, bacterial

Catheter related sepsis (CRS) surveillance in an ICU

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Surveillance of hospital acquired infection reduces incidence when relevant data are fed back to clinicians.[1] Surveillance of catheter related sepsis (CRS) has been ongoing in our ICU since May 1996. CRS decreased from 4.79 per 1000 occupancy days to 1.4 per 1000 days with monthly feedback to ICU staff. We describe the methodology

All blood culture results (positive and negative) were reported via a printout to the ICU on a weekly basis. Using standard definitions[2] the ICU and microbiologist assessed the result to determine if the outcome was one of the following: (a) blood stream infection, (b) catheter related sepsis or (c) ICU acquired CRS.

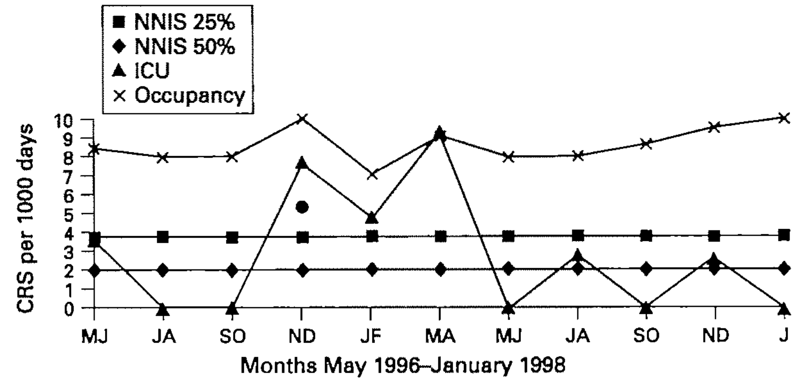

Figure 5 Catheter related sepsis (CRS) in the ICU per 1000 days (excluding burns patients).

Occupancy data were provided by the operations manager. The NNIS surveillance results were used for comparison.[3] Monthly feedback to an anaesthetist and sister was established. Daily central device use data were collected.

For the first 6 months the CRS incidence density was less than the NNIS 25% (1.14). However, the second 6 months yielded results above the NNIS median graph (fig. 5). The first feedback was completed by April 1997. Device utilistion for 35 days was 100%.

At least 9 months' data are needed to determine a true CRS rate. In our ICU occupancy data were a good proxy for device use. CRS appears to be more likely when the ward is busy. Surveillance with feedback reduced incidence.

Keywords: intensive care, audit; complications, sepsis

References

1. Haley RW. *American Journal of Epidemiology* 1985; 121: 182.
2. National Nosocomial Infection Surveillance (NNIS) Report. Data Summary from Oct 1986–April 1997, issued May 1997.
3. The Nosocomial Infection National Surveillance Scheme. Report of the Pilot study for the module for the surveillance of hospital acquired bacteraemia. *PHLS* (UK) July 1997.

Plasma antioxidant activity towards phospholipid hydroperoxide is reduced in septic shock

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In various diseases, products of oxidative stress create a great problem for the body's defence mechanism. Protection against damaging products, such as lipid hydroperoxides, is an essential process.[1,2]

We have examined the ability of plasma, from normal and septic shock subjects, to detoxify a phospholipid hydroperoxide Reduction of the phospholipid hydroperoxide, 1-palmitoyl-2-(13-hydroperoxy-*cis*-9, *trans*-11-octadecadienoyl)-L-3-phosphatidylcholine (PLPC-OOH)[3] was determined using a sensitive and specific high performance liquid chromatography (HPLC) method.[4] The free sulphydryl (SH) content of each plasma sample was also measured by titration with 5,5'-dithiobis (2-nitrobenzoic acid).[5] Mean activity and free SH content of plasma from 18 normal and 15 septic shock subjects are shown in table 16.

The plasma antioxidant activity of septic patients on the phospholipid hydroperoxide was lower than the plasma activity from normal subjects; sulphydryl content was also less than 50%. However, the specific activity on phospholipid hydroperoxide was not reduced; both the septic and normal plasma samples were capable of reducing 0.05 nmol PLPC-OOH/min/mg of protein.

Table 16 Mean activity of PLPC-OOH and free sulphydryl (SH) content of each plasma sample from 18 normal and 15 septic shock subjects

Plasma type	Activity towards PLPC-OOH (nmol/min/ml plasma)	Free SH content (μmol SH/ml plasma)	Human serum albumin (mg ml^{-1})
Normal	3.62 (0.95)	0.46 (0.04)	55 (3)
Septic	2.28 (0.67)	0.19 (0.07)	25 (11)

We have found previously that human serum albumin is responsible for the majority of the activity towards PLPC-OOH in plasma. Thus the difference between the normal and septic plasma samples may be attributed to a loss of albumin, with no change in the quality of the remaining albumin.

Overall, the results showed that septic shock patients have decreased protection against plasma phospholipid peroxidation. The clinical value of maintaining plasma antioxidant potential by modification of albumin and sulphydryl contents in septic shock subjects has yet to be established.

Acknowledgement

We thank the Biotechnology and Biological Research Council for funding the project.

Keywords: complications, septic shock

References

1. Kagan VE. *Lipid peroxidation in Biomembranes*. CRC Press, 1988; 2–11.
2. Halliwell B, Gutteridge JMC. *Methods in Enzymology* 1990, **186**: 1–85.
3. Maiorino M, Gregolin C, Ursini F. *Methods in Enzymology* 1990; **186**: 448–457.
4. Bao Y, Chambers SJ, Williamson G. *Analytical Biochemistry* 1995; **224**: 395–399.
5. Ellman G, Lysko H. *Analytical Biochemistry* 1979; **93**: 98–102.

Functional iron deficiency in critical illness

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Functional iron deficiency (FID) has been described in renal failure, nutritional deficiency and chronic ill health. An approach to assessment of FID has been proposed by MacDougal and colleagues.[1] We have used this to quantify FID in patients presenting to the intensive care unit (ICU), in an attempt to assess its consequences on outcome.

Fifty-one sequential adult patients presenting to the ICU were studied. Exclusion criteria were massive transfusion (>8 u.), pregnancy and age >80 yr. Patient characteristics included age, APACHE II score, "elective" *vs* "emergency" admission. We measured admission and subsequent (3 daily) ferritin concentrations, haemoglobin and FID (proportion of hypochromic red blood cells measured by flow cytometry). Primary outcome variable was duration of ICU stay, and secondary variables included hospital stay and mortality. Results, expressed as median (interquartile range) or mean (95% confidence interval) as appropriate, were analysed by Kaplan–Meier analysis, Fisher's exact test and Mann–Whitney *U* test.

FID was present in 35% (95% CI 22–48%) of patients at ICU admission, as defined by more than 10% of red blood cells exhibiting hypochromasia. Comparing FID and non-FID patients, emergency admission (15/18 *vs* 23/33), age (60.5 (48–74) *vs* 59 (42–67) yr), ferritin (342 (66–703) *vs* 292 (132–1640)), haemoglobin (10.7 (9.3–11.5) *vs* 10.8 (9.4–12.1)) and APACHE II score (18 (14.5–24) *vs* 18.5 (11–25)) were similar in the two groups (ns). Mean ICU stay was 7.6 (95%CI 4.4–10.8) *vs* 3.3 (2.0–4.5) days (P<0.0007) (fig. 6).

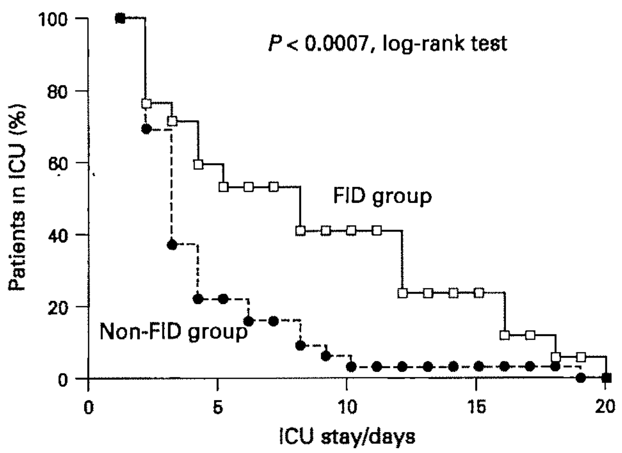

Figure 6 Mean duration of ICU stay in the functional iron deficiency (FID) and non-FID groups.

FID is seen in critically ill patients presenting to intensive care. FID could not be detected on the basis of haemoglobin or serum ferritin. Severity of FID correlates with duration of ICU stay. Further work is required to assess the effect of FID on organ system failures and its correction on outcome.

Keywords: complications, iron deficiency; intensive care, audit

Reference

1. MacDougal IC, Cavill I, Hulme B, Bain B, McGregor E, McKay P, Sander E, Coles GA, Williams JD. *British Medical Journal* 1992; 304: 225–226.

Potent fibroproliferative growth factors are present in bronchoalveolar lavage fluid at the onset of the acute respiratory distress syndrome

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Interstitial and alveolar fibrosis is a significant cause of mortality in the acute respiratory distress syndrome (ARDS) with a doubling of lung collagen content observed in patients surviving more than 2 weeks.[1] Current hypotheses propose fibroproliferation as a late event in ARDS. However, the temporal relationship between the onset of fibroproliferation and the clinical course of ARDS is far from clear and the profibrotic factors which drive this process are not identified.

In contrast with current dogma, we hypothesized that fibroproliferation is occurring at the earliest stages of ARDS and that fibroblast growth factors such as thrombin would be detectable in bronchoalveolar lavage fluid (BALF) at this time point. Patients fulfilling the ERS/ATS consensus criteria for ARDS underwent BAL within 48 h of onset. The mitogenic activity of this BAL fluid on human fetal lung fibroblasts (HFL-1) was assessed by incubating cells for 48 h with serial dilutions of the lavage.

Initial studies in seven patients demonstrate that in all cases BALF from this time was mitogenic for fibroblasts with a mean of 62% (range 28–119%) stimulation above control at a 1:16 dilution This compares with 49.7%, 26.8% and 45.4% stimulation in patients with systemic sclerosis, idiopathic pulmonary fibrosis and sarcoidosis, respectively, and is the highest mitogenic activity we have so far detected in BALF from any interstitial lung disease. Control lavage did not stimulate fibroblast proliferation.

These data support the hypothesis that fibroproliferative factors are present in BALF from the onset of ARDS, suggesting fibroproliferative and inflammatory events are occurring in parallel rather than in series. This hypothesis is supported further by a study of procollagen peptide III (a marker of collagen turnover) which is increased within the first 24 h of ARDS.[2] We are currently identifying the growth factors responsible in sequential BALF samples.

Keywords: lung, adult respiratory distress syndrome

References

1. Zapol WM, Trelstad RL, Coffey JW, Tsai I, Salvador RA. *American Review of Respiratory Diseases* 1979; 119: 547–554.
2. Chessnutt AN, Matthay RA, Tibayan FA, Clark JG. *American Journal of Respiratory and Critical Care Medicine* 1997; 156: 840–845.

Acute brain injury: quantifying neuro-metabolic changes using chemical shift magnetic resonance imaging

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Defining the extent of acute brain injury from trauma (TBI) or subarachnoid haemorrhage (SAH) has important implications for neuro-intensive care management and prognosis. Diagnosing diffuse axonal injury and central brain lesions is becoming easier with MRI; spectroscopic imaging (SI) using chemical shift imaging (CSI) allows construction of a metabolic map in selected brain volumes of interest (VOI) which may indicate areas of occult neuronal injury. Our study uses CSI to investigate the acute period following brain injury.

Nine patients were studied (seven males), aged 18–64 yr (mean 38 yr). Seven patients with severe TBI (GCS<8), one with moderate TBI (GCS 9) and one with delayed ischaemic deficit from SAH were admitted to the intensive care unit and received treatment according to our standard protocols to reduce secondary insults to the brain. In five patients whose lungs were ventilated and in four who breathed spontaneously (discharged from ITU) T2 and CSI imaging were performed, 4–26 days (mean 13 days) after injury using a Siemens 63 SP 1.5 Tesla Magnetom scanner. Spectra (fig. 7) were generated for each of the 20 voxels (volumes)

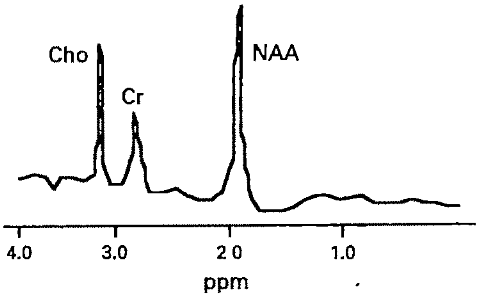

Figure 7 Spectra generated for each of the 20 voxels within the VOI, and from the area under the curves a metabolite map was constructed for N-acetyl aspartate (NAA), choline (Cho) and creatine[1] (Cr); three metabolite concentration areas were compared.

within the VOI, and from the area under the curves a metabolite map constructed for N-acetyl aspartate (NAA), choline (Cho) and creatine[1] (Cr); three metabolite concentration areas were compared: areas of injury on T2 *vs* contralateral area *vs* control.

The Mann–Whitney test showed significant differences in the concentration of NAA between the lesion and control ($P<0.002$), and between the contra-lateral area and control ($P<0.02$). Two sample *t* tests failed to show a difference between NAA in the lesion and contralateral areas ($P=0.055$), and there were no significant differences in concentrations of the other metabolites although choline in the lesion compared with the control approached statistical significance ($P=0.064$). We could not demonstrate a lactate peak in any of the patients.

This is the first report of CSI in acute brain injury and we have demonstrated a significant reduction in neurone specific NAA both in areas where there is a visible lesion and apparently normal areas with occult injury. CSI allows accurate measurement of brain metabolites, specific regions of interest within the VOI can be delineated and calculated separately—a property unique to this technique. NAA is found only in neurones and is reduced in areas of neuronal damage.[1] Choline is the breakdown product of cell walls, and creatine is involved in cell energy transfer. It may be possible to use this technique to guide therapy, monitor recovery[2] and aid outcome prediction.

Acknowledgement

Project funded by a grant from the MRC.

Keywords: brain, injury; monitoring, magnetic resonance imaging

References

1. Wild JM, Marshall I. *Magnetic Resonance Imaging.* 1997; **15:** 1057–1069.
2. Prescuitti O, Tarducci R, Gobbi G, Pelliccioli GP, Todeschini E, Franceschini M, Zampolini M. *Abstracts of the 5th Scientific Meeting of ISMRM* 1997; 1230.

Agreement and artefact: measuring ICP during MR imaging

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This is the first report on the function and image artefact generation of an intracranial pressure monitor Codman microsensor/ Johnson & Johnson Professional, Inc. Randolph, MA, USA) in a magnetic resonance scanner. We have investigated the function of the Codman ICP monitor within an MRI scanner during T2 weighted, spectroscopy, and diffusion weighted imaging sequences, and quantified image artefact generation.

The Codman ICP monitor has three parts: strain gauge transducer, standard 3-m connector cable and the display unit "express box". In the MRI scanner the express box must be kept distant from the magnet, and therefore a longer 12.5-m connector cable was used. A water manometer was used as the standard to generate pressure and was used to test the 3-m and 12.5-m cable outwith the MR scanner. We then tested the Codman ICP monitor in the MR scanner with the express box exposed to a 3-m Tesla magnetic field 4.5 m from the isocentre of the 1.5 T magnet while running three types of sequence: (1) T2 weighted, (2) spectroscopy and (3) diffusion weighted imaging. The second assessment of the Codman ICP monitor was to ascertain the artefact generation on T2 imaging of a volunteer. A baseline T2 image was obtained then repeated three times; on each occasion another piece of Codman equipment was added: (a) transducer (taped to the forehead), (b) 12.5-m connector cable and (c) express box. The images were each assessed for quality visually by a blinded consultant neuroradiologist, and by calculating the signal to noise ratio.

Taking the water column as the standard there was excellent agreement for comparisons of water with the Codman (using the standard 3-m and the 12.5-m connector cables (limits of agreement <3.5 mm Hg)). In the MR scanner running the three types of sequence (T2 weighted, spectroscopic, and diffusion weighted imaging (DWI)) and using the Codman with 12.5-m cable the agreement was good for each type of scan sequence between the water column and the Codman value (limits of agreement <5.5 mm Hg), except during DWI (limits of agreement <14 mm Hg). The visually assessed quality of the volunteer T2 weighted images were excellent for the baseline, transducer and transducer with 12.5-m connector cable. The image produced with the whole Codman ICP monitor (transducer, 12.5-m connector cable and express box) was grainy but interpretable. The calculated signal:noise ratio of the scan with the whole Codman was reduced by 60% compared with the control and other two scans.

The Codman ICP monitor has been shown to have a rapid response, reliability,[1] accuracy and stability over time. It is relatively straightforward to perform CT scans on acutely brain injured intensive care patients. In the strong magnetic field of a magnetic resonance scanner, monitoring equipment must be made specially or converted to function in such an environment. Knowledge of this equipment and of the hazards a magnetic environment creates is mandatory for anyone involved in anaesthetizing patients in MRI. We have shown that it is safe to use the output from the Codman ICP monitor to guide patient management while in the MR scanner, and that the MRI images obtained are acceptable for clinical purposes.

Keywords: monitoring, magnetic resonance imaging, brain, intracranial pressure

Reference

1. Gray WP, Palmer JD, Gill J. *Neurosurgery* 1996; 39: 927–932.

Acute brain injury and the ECG: QT dispersion is increased

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For many years it has been known that patients develop ECG changes after subarachnoid haemorrhage (SAH). We have analysed the admission ECG of 21 patients with SAH and 15 patients with traumatic brain injury (TBI) for simple abnormalities and QTc dispersion[1]—a quantitative measure of myocardial repolarization and the difference in QT duration of the longest minus the shortest QT interval, corrected for heart rate, of a 12-lead surface ECG. A large dispersion indicates an arrhythmogenic potential, and it may be influenced by catecholamines.

Patients with acute brain injury admitted to the ITU had ECG performed within 24 h of admission. These ECG were analysed for simple abnormalities—rate, rhythm, axis, block, conduction, p-wave, QRS, ST segment and T-wave changes. One point was given for each abnormality. The QTdc (ms) was calculated for each ECG using a standard digitizing board.[2]

We analysed the ECG of 21 patients with SAH (five males) mean age 34 yr, and 15 patients with TBI (12 males), mean age 49 yr. In total, 26 of 36 patients with acute brain injury (72%) clearly demonstrated simple ECG abnormalities. In the SAH group, 13 of 21 patients (62%) had simple ECG changes with scores ranging from 0 to 6 (median 1). Thirteen of 15 TBI patients (87%) also had simple ECG changes with a score of 0–4 (median 2). There was no significant difference in ECG scores between the two groups. QTdc was very prolonged in both groups (normal <50 ms). In SAH, mean Qtdc was 90 ms, compared with 81 ms in TBI (ns). Of the SAH patients, seven developed neurogenic pulmonary oedema (NPO) and mean QTdc was 94 ms compared with 85 ms in the SAH patients who had no NPO (ns). Comparing ECG score with QTdc, there was no difference in the means of each score group (fig. 8), including ECG with a score of zero. In this group with apparently normal ECG, mean QTdc was 81 ms.

An increased QTdc predisposes to arrhythmias and a value of less than 50 ms is found in healthy individuals. When prolonged it predicts sudden death in patients with chronic heart failure,[3] diabetes and renal failure—presumed to be a result of arrhythmias. Myocardial depression and arrhythmias may cause serious secondary insults to the injured brain.[4] We have confirmed the ECG changes reported many times in SAH, and shown that a traumatic insult to the brain results in similar ECG changes, perhaps mediated via catecholamine release. It has been suggested that under

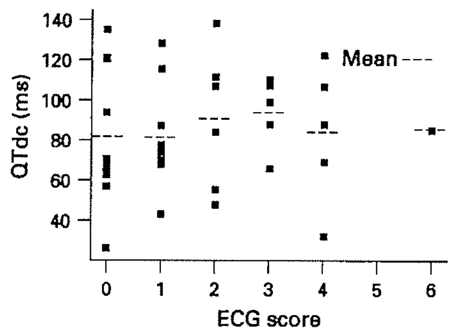

Figure 8 ECG score *vs* Qtdc.

the influence of neurohormonal changes and alterations in autonomic tone, QT dispersion is prolonged.[1] We have demonstrated QTdc to be prolonged in this population not only in those with abnormal ECG but in those with ECG which appear completely normal.

Keywords: monitoring, electrocardiography; brain, injury

References

1. Higham PD, Campbell RW. *British Heart Journal* 1994; 71: 508–510.
2. Campbell RW, Gardiner P, Amos PA, Chadwick D, Jordan RS. *European Heart Journal* 1985; 6: (Suppl. 3).
3. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. *Lancet* 1994; 343: 327–329.
4. Miller JD Sweet RC, Narayan R, Becker DP. *Journal of the American Medical Association* 1978; 240: 439–442.

An observational study of the incidence of myocardial injury in the ICU using daily estimations of troponin I, CK MB, myoglobin and daily ECG

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Increased cardiac troponin I (cTnI) is a highly specific and sensitive marker of myocardial damage and may allow recognition of lesser degrees of myocardial injury. We compared cTnI with ECG and CK MB concentrations in the detection of myocardial injury in an unselected series of medical and surgical ICU patients.

Information on patient characteristics was collected. Baseline heart rate, arterial pressure, heart rhythm and use of inotropic agents were recorded prospectively by nursing staff on a daily basis. Daily ECG were recorded and read on the same day. Blood specimens for estimation of myoglobin, CK MB and cTnI concentrations were collected each day and analysed at the end of the study period. We studied 109 consecutive admissions to the ICU of the Victoria Infirmary, Glasgow.

Of the 109 patients (55 females), 60 were admitted from theatre and 49 from other areas of the hospital. Median age was 68 (interquartile range 50.25–74.75) yr. Median APACHE II score for the 98 individuals who had scores calculated was 19 (range 3–42). SMR by APACHE III for our patient cohort was 0.98. ECG abnormalities (development of LBBB or ST segment depression >1 mm or T inversion in two leads or more) developed in 56% (61 of 98) of patients during ICU admission. cTnI concentrations were increased in 70.6% (77 of 109) of our patients (normal <0.1 g litre^{-1}). In 44% (48 of 109) of cases, cTnI concentrations were >0.5 g litre^{-1} (0.5 g litre^{-1} is the laboratory threshold value for diagnosing acute myocardial infarction). All subjects in an unmatched control group of "non-cardiac" in-patients consisting of 41 males (median age 62 yr) and 57 females (median age 70 yr) had cTnI concentrations of <0.1 g litre^{-1}. Also, all subjects in a second control group of 46 females (median age 32 yr) and 12 male volunteers (median age 42 yr) had cTnI concentrations of <0.03 g litre^{-1}. Of those with increased cTnI concentrations, 70 had ECG. Seventy percent (49 of 70) of this group developed ECG abnormalities. Myoglobin concentrations were increased in 91% (99 of 109) of our patients (normal <70 g litre^{-1}); 71 5% (78 of 109) had increased CK MB concentrations (normal <5 g litre^{-1}). ECG were available for 70 of the patients with increased CK MB concentrations and within this group 70 % (49 of 70) developed abnormalities at some stage. While in the ICU 42 of 98 (42.8%) patients had both ECG abnormalities and increases in CK MB and cTnI concentrations.

Using the cardiac specific cTnI assay, we found a 70.6% incidence of myocardial injury in our ICU population which exceeds the 15% observed in two American medical ICU.[1,2] A total of 70% of individuals with increased cTnI concentrations developed ECG changes

Acknowledgement

The laboratory test kits were provided by Beckman Instruments (UK) Ltd.

Keywords: monitoring, electroencephalography; heart, myocardial function

References

1. Guest TM, Ramanathan AV, Tuteur PG, Schechtman KB, Ladenson J, Jaffe AS. *Journal of the American Medical Association* 1995; 273: 1945–1949.
2. Kollef M, Ladenson TH, Eisenberg PR. *Chest* 1997; **111**: 1340–1347.

An audit of mortality for combined renal and respiratory failure in Scottish ICU

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We attempted to define mortality for combined renal and respiratory failure in Scottish intensive care units (ICU) and to compare outcomes across units with widely varying levels of dialysis activity.

This was a retrospective audit of 11 ICU, representing 78% of units in Scotland undertaking dialysis. Patients undergoing dialysis and ventilation were identified from daily entry of therapeutic intervention scoring system data (TISS). Outcome was identified by survival at ultimate hospital discharge and severity of illness on first admission to the ICU determined by the acute physiology and chronic health evaluation score (APACHE II) All patients identified as undergoing both ventilation and dialysis had this confirmed by case-note review. For a 2-yr period between 1995 and 1997, we validated 470 incidences of combined renal and respiratory failure (defined by the need for both dialysis and ventilation).

When data were obtained directly from the database, 922 patients were identified with a hospital mortality of 48.3%, considerably lower than that reported previously. Following the validation process, 470 patients were identified with a hospital mortality of 64%, which compares with a predicted mortality (based on their first 24 h in the ICU) of 52.6%. Table 17 shows the results as number of patients dialysed in each ICU during the study period With the exception of the unit which dialysed only one patient (Unit A), mortality varied between 50% and 74.3% with no obvious relationship between observed mortality or standardized mortality ratio (SMR) and number of patients dialysed. Of the eight most common admission diagnoses, septic shock and pneumonia resulted in the worst outcome. Duration of dialysis did not influence the observed outcome.

Scottish ICU demonstrate a wide range of dialysis activity. In spite of this, overall mortality for patients with combined renal and respiratory failure was as good as that described previously.[1,2] There was no obvious relationship between number of patients dialysed and outcome. This suggests that no improvement in quality of patient care for this high-risk group could be produced by further centralization of care for such patients.

Acknowledgement

Funding from the Clinical Resource and Audit Group (CRAG).

Keywords: intensive care, audit; kidney, function; lung, function

References

1 Simpson HKL, Allison MEM, Telfer ABM. *Renal Failure* 1987; 10: 45–54.

Table 17 Number of patients, and observed and predicted mortality for each ICU

	Unit										
	A	B	C	D	E	F	G	H	I	J	K
No. of patients	1	13	16	18	22	30	34	35	81	82	138
Obs. mort. (%)	100	62	50	56	68	67	53	74	64	65	65
Pred. mort. (%)	21	61	53	46	56	54	51	52	52	55	52
SMR	4.7	1	1	1.2	1.2	1.3	1	1.4	1.2	1.2	1.3

2. Gillespie DJ, Marsh HMM, Divertie MB, Meadows JA. *Chest* 1986; **90**: 364–369.

Portable ultrasound for difficult central venous access

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Central venous catheterization is a common invasive procedure with a diverse range of complications. Early complications are often related to blind needle insertion. Morbidity and mortality from needle insertion is likely to be under-reported. Ultrasound guidance has been shown to improve successful catheter placement and reduce complications compared with surface marking placement.[1] Patients in whom central venous catheterization (CVC) can be considered more difficult than usual regularly present from intensive care, renal and haematology units. We identified patients with anticipated "difficult" CVC using the following criteria: coagulopathy (including low platelets); altered surface anatomy; abnormal vascular anatomy; limited sites for access; previous multiple punctures or sites required; and previous complications.

Patients were examined by intensive care staff at the bedside with a portable ultrasound (US) machine with a 7.5-MHz linear array probe (Scanner 100; PIE Data UK Ltd). Internal jugular, subclavian and femoral veins (six sites) were scanned with the patient supine and their head in the neutral position. We aimed to determine the following: (1) optimum sites for access (influenced by distensibility of veins during valsalva or head down and relation to nearby structures such as arteries); (2) reasons for previous failures and/or complications (very small vein, thrombus, etc.).

Information gained could then be used to enhance confidence in the operator using traditional surface landmark technique or real-time ultrasound guidance could be used. Thirteen patients (eight males; aged 29–79 yr) were examined. Eight (62%) patients fulfilled three or more criteria for anticipated "difficult" CVC. In six (46%) patients, CVC at two or more sites had previously been attempted. In five of these (83%), US provided a probable cause for failure (e.g. very small vessel, thrombus). Four patients had all six sites available by clinical judgement but only one patient had all sites deemed suitable by US. In two patients, US led to *in situ* lines being re-wired as other sites were considered unsuitable. Of the 13 patients, one refused further attempts at CVC after US examination. In the remaining 12 patients first pass CVC was successful in 10 (83%). Two and three passes were required in two patients. These two patients had complications associated with venepuncture (artery punctured; two sites required).

Portable ultrasound is simple, safe and quick. In cases of "difficult" CVC it can explain previous failures and complications. It enables the optimum site for further attempts to be chosen. A high first pass success rate is achieved if attempts are US or surface landmark guided. These findings are similar to those found by other investigators using US in difficult cases of central venous access.[2]

Keywords: complications, catheter misplacement; measurement techniques, ultrasound

References

1. Randolph AG, Cook DJ, Gonzales CA, Pribble CG. *Critical Care Medicine* 1996; 24: 2053–2058.
2. Gallieni M, Cozzolini M. *International Journal of Artificial Organs* 1995; 18: 117–121.

Portable ultrasound before percutaneous tracheostomy

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Percutaneous dilatational tracheostomy (PDT) is a common and safe procedure. However, concerns exist regarding bleeding and para-tracheal placement of the tracheostomy tube during blind needle and dilator insertion.[1] Our experience is that bleeding is uncommon and usually occurs from an anterior jugular vein (AJV) or inferior thyroid vein (ITV). Rare instances of para-tracheal placement of the tracheostomy tube have been recognized before serious complications ensue. Ultrasound (US) has been used to define underlying anatomy before open surgical tracheostomy.[2] Given the blind nature of PDT, prior identification of anterior neck structures using US is attractive.

We examined prospectively 11 patients undergoing PDT on the intensive care unit using a portable ultrasound scanner with a linear array 7.5-MHz probe (Scanner 100; PIE Data UK Ltd). We assessed the pre-tracheal anatomy in general with specific attention as to the presence of AJV and ITV. We also assessed whether the portable scanner could be used to identify the midline of the trachea and so aid in correct placement of serial dilators.

All patients were previously consented for PDT. They were sedated, paralysed and positioned supine with a firm pillow under their shoulders. Patients were then examined before PDT for blood vessels and at intervals during PDT to assess dilator position relative to the trachea. The trachea was identified easily in all cases and its midline direction was marked on the skin surface. There were no complications (table 18).

Portable US provides a simple, safe and quick method of assessing anterior neck anatomy before PDT, in particular for the presence of veins vulnerable to injury. Extra vigilance can then be used during blunt dissection or the vein can be electively tied off. US also enables the midline and approximate level for tracheal puncture to be chosen. This may be of particular importance in patients with poor surface landmarks to guide the procedure.

Keywords: measurement techniques, ultrasound; surgery, tracheostomy

Table 18 Pre-tracheal anatomy, assessed using ultrasound. AJV=Anterior jugular vein; ITV=inferior thyroid vein

AJV seen	8/11	(73%)	AJV considered vulnerable	3/8	(38%)
Thyroid isthmus seen	9/11	(82%)			
ITV seen	3/9	(33%)	ITV considered vulnerable	3/3	(100%)
Vulnerable artery seen	2/11	(18%)			

References

1. Petros S, Engelman L. *Intensive Care Medicine* 1997; **23** 630–634.
2. Bertram S, Emshoff R, Norer B. *Journal of Oral and Maxillofacial Surgery* 1995; 53: 1420- 1424.

Tracheostomy in the intensive care unit (ICU): things have changed

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Patients in the ICU require a tracheostomy for a variety of indications: long-term ventilation, to aid weaning or to protect the airway. Since its introduction, percutaneous tracheostomy (PT) has become increasingly popular. It has several advantages and our experience confirms the short-and long-term safety of the procedure.[1,2] PT was introduced at our hospital in 1991.

We audited our practice to determine: (1) if more tracheostomies were being undertaken since the introduction of PT in our hospital and (2) what were the implications for training. Details of all tracheostomies performed at Frenchay in the last 13 yr were collected from theatre registers, the hospital PAS system, ICU database and an ICU procedure book.

We found that the proportion of ICU patients undergoing tracheostomy increased from a median of 9 0% (range 5.6–9.4%) before PT introduction to 18.3 (range 10.9–21.6)% in recent years ($P<0.01$). Since the introduction of PT, the number of formal tracheostomies performed has greatly decreased reducing the opportunities for training of surgical trainees (fig. 9). Of the 474 PT undertaken, only 16 were performed by surgical trainees, the remainder by anaesthetic/ICU staff.

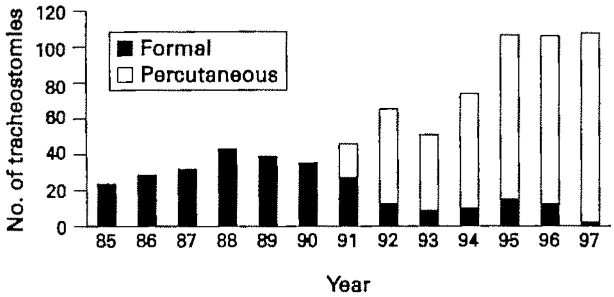

Figure 9 Number of formal and percutaneous tracheostomies performed in the ICU from 1985 to 1997.

We conclude that the introduction of PT increased the proportion of patients undergoing tracheostomy in the ICU, despite no change in case-mix This could reflect an under utilization of tracheostomy in the past, or a relaxation of the indications for the procedures at present. The opportunities for surgical trainees to learn formal tracheostomy has been significantly decreased. They should be offered the chance to learn PT techniques.

Keywords: intensive care, audit; surgery, tracheostomy

References

1. Manara AR. *British Journal of Oral and Maxillofacial Surgery* 1994; 32: 155–160.
2. Law RC, Carney AS, Manara AR. *Anaesthesia* 1997; 52: 51–56.

Determination of gastric mucosal $P\text{CO}_2$: arterial $P\text{CO}_2$ difference (CO_2 gap) needed to produce a mucosal pH (pHi) of 7.32 in the presence of normal systemic pH

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A pHi of 7.32 is recognized to be the lower limit of normal[1] and pHi values <7.32 have been shown to have predictive value for morbidity and mortality in critically ill patients.[2] The CO_2 gap, as a marker of splanchnic oxygenation, has advantages over pHi in that it is unaffected by systemic acid–base balance.[3] The object of the study was to determine the CO_2 gap required to produce a calculated pHi of 7.32 in the presence of a normal systemic pH (pHa).

Fifty cardiac surgery patients were studied for the first 8 h after surgery. Gastric mucosal P_{CO_2} (Pr_{CO_2}) was monitored using gastric tonometers (Trip catheters, Tonometrics Inc, USA) connected to regional capnometry monitoring (Tonocap, Datex, Finland). Gastric pHi and CO_2 gap were calculated at 2-hourly intervals using the formulae: $\text{pHi}=\text{pHa}-\log(Pr_{\text{CO}_2}/Pa_{\text{CO}_2})$ and $Pr_{\text{CO}_2}-Pa_{\text{CO}_2}$, respectively. All patients received ranitidine both before and after operation. Paired readings of CO_2 gap and pHi associated with a pHa ≥ 7.36 and ≤ 7.45 were noted and linear regression analysis was performed as shown. The $[\text{H}^+]$ corresponding to a pHi of 7.32 (48 nmol litre^{-1}) was substituted into the equation for the line of best fit and the CO_2 gap calculated.

Seventy-nine paired readings of CO_2 gap and pHi were obtained when pHa was ≥ 7.36 and ≤ 7.45. The CO_2 gap to produce a pHi of 7.32 was found to be 0.94 kPa (fig. 10).

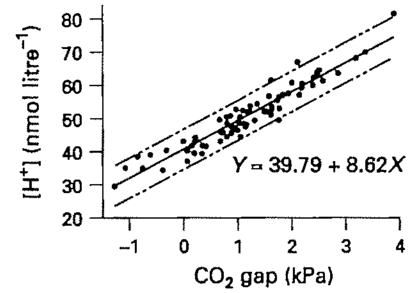

Figure 10 Linear regression analysis of CO_2 gap and calculated mucosal $[\text{H}^+]$.

A CO_2 gap rise of greater than 0.9 kPa was required to produce a calculated pHi of <7.32 in the presence of a normal arterial pH.

Keywords: gastrointestinal tract, pH; carbon dioxide, partial pressure

References

1. Heard SO, Helmsmoortel CM, Kent JC, Shahnarian A, Fink MP *Critical Care Medicine* 1990; 19: 271–274.
2. Mythen MG, Purdy G, Mackie IJ, McNally T, Webb AR, Machin SJ. *British Journal of Anaesthesia* 1993; 71: 858–863.
3. Schlichtig R, Mehta N, Gayowski TJP. *Journal of Critical Care* 1996; 11: 51–56.

Use of transoesophageal Doppler to derive cardiac output in ventilated children

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Transoesophageal Doppler (TOD) is used for continuous haemodynamic monitoring of critically ill adults. Flow velocities measured in the descending aorta expressed as minute distance (MD) can be used to derive cardiac output (CO) when combined with a proportionality constant. We wished to investigate the usefulness of TOD in children with a view to the creation of a paediatric nomogram for CO values, and to quantify the accuracy ofTOD in measuring changes in CO after fluid administration.

We studied 60 sedated children undergoing ventilation, median age 40 months (range 7 days to 16 yr) and median weight 14 (3–60) kg Patients with aortic arch abnormalities and residual shunt were excluded. A 5.5-mm diameter, 4-MHz, flexible TOD probe (EDM Deltex Medical, Chichester) was placed into the distal oesophagus and fixed. Stroke distance, averaged over 10 cycles was used to calculate MD. Concurrently CO was measured using femoral artery thermodilution (FATD) (COLD Z-021 Pulsion, Munich, Germany). Five consecutive measurements using both modalities were made, and both averaged. Following this, a bolus of 4.5% albumin was given (5–10 ml kg^{-1}) and measurements repeated, giving a total of 120 paired, averaged measurements for analysis.

FATD cardiac index ranged from 1.4 to 9.0 (median 4.0) litre min^{-1} m^{-2}, with CO ranging from 0.3 to 9.2 (median 2.8) litre min^{-1}. Mean coefficients of variation were 3.7% for MD and 5.0% for FATD.

For derivation of the regression equation, the square of patient length (cm) (l^2) was used, as length correlates closely with aortic root dimensions throughout childhood. Regression analysis yielded the following equation: $y=0.667x+0.727$, $r^2=0.811$, standard error of estimate (SEE)=0.91, where y=estimated CO and $x=(\text{MD}\times l^2/10^7)$.

Analysis of standardized and studentized deleted residuals, leverage and Cook's distance revealed no serious outliers, however a raw residual plot suggested unequal variance. To stabilize the variance, natural logarithmic transformation of both variables was undertaken, which effectively preserved the linear relationship between the two variables. This gave the new regression equation: $y=0.813x+0.129$, $r^2=0.900$, SEE=0.27, where: y=ln (estimated CO), $x=\ln(\text{MD}\times l^2/10^7)$, 0.129=ln (intercept), 0.813=slope, which is equivalent to the power function model: estimated $\text{CO}=1.138\times(\text{MD}\times l^2/10^7)^{0.813}$. Bland Altman analysis, undertaken to ascertain if TOD was able to follow changes in CO following a fluid bolus, gave a mean bias of 1.2% with limits of agreement (1.96×SD) of ±21.5%.

TOD is accurate enough for clinical purposes to both measure cardiac output and to follow changes in cardiac output in critically ill children of all ages. As such, it represents an important non-invasive tool for haemodynamic monitoring.

Keywords: measurement techniques, transoesophageal Doppler; heart, cardiac output

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Influence of dopexamine on the duration of postoperative colonic inhibition in patients undergoing planned colorectal surgery

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Temporary stasis in gastrointestinal function is a known consequence of major abdominal surgery. Mucosal damage is proportional to the time required to establish enteral feeding after operation. Dopexamine acts as an agonist at ß2 and DA1 adrenoreceptors both found in the GI tract and preferentially vasodilate hepatosplanchnic vessels. Our hypothesis was that this restores early gut motility.

Twenty patients undergoing left-sided large bowel resections were randomized prospectively before surgery to receive a infusion of dopexamine 2 µg kg^{-1} min^{-1} or placebo. The infusion was started after induction of anaesthesia and continued for the duration of the surgery and for up to 24 h after operation. All patients had a transoesophageal Doppler probe paced before surgery to continuously monitor and optimize their cardiovascular status to maintain a cardiac index of at least 2.5 litre min^{-1} m^{-2}.

Colonic motility was monitored using radiopaque rings, contained in a capsule ingested 12 h before surgery. Abdominal radiographs were obtained immediately after surgery, 24 h after surgery and then every 12 h until propagative colonic motility was proved in two consecutive films. To comply with radiation safety, no more than nine radiographs were obtained. Motility was defined as the propulsion of at least 25% of the markers from one colonic area to the other.[1]

Three patients did not complete the study; their data were not analysed. There was no statistically significant difference in colonic motility between the dopexamine and placebo groups. However hospital stay in the dopexamine group was statistically shorter (table 19).

As a pilot, this study did not show a significant difference or a clear trend to warrant a larger study. The finding of shortened stay is in line with other studies,[2] concluding that cardiac optimization and enhancement of splachnic perfusion could improve the outcome of surgical patients and may cause speedy recovery.

Table 19 Colonic motility and hospital stay in the dopexamine and placebo groups. No significant differences

	Dopexamine	Placebo
Colonic motility (min)	5696 (95% CI)	4752 (95% CI)
Hospital stay (days)	10.0 (95% CI)	15.6 (95% CI)

Acknowledgement

Supported in part by a grant from Speywood Pharmaceuticals Ltd.

Keywords: surgery, colorectal; gastrointestinal tract, bowel function

References

1. Tollesson PO, Cassuto J, Faxen A, Bjork L. *Scandinavian Journal of Gastroenterology* 1991; 26. 887–896.
2. Sinclair S, James S, Singer M. *British Medical Journal* 1997; 315: 909–912.

A comparative study of the incidence of nosocomial colonization in patients with closed suction catheter changes at 24 *vs* 48 h

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It is now generally accepted that ventilator circuitry can be used safely for more than 48 h without increasing the incidence of nosocomial pneumonia.[1 2] The closed suction system is considered to be part of the ventilator breathing system and has been changed historically at 24 h. Since the closed suction catheter becomes a part of the ventilator system it should be possible to change it less frequently than every 24 h. We have compared the rates of nosocomial colonization in patients who have had closed suction catheters in situ for 24 *vs* 48 h.

A total of 73 patients were allocated randomly to have their closed suction catheter changed at either 24 or 48 h. Sputums on admission, at 24 and 48 h, and suction catheter tips at 24 and 48 h were sent for quantitative culture.

Chi-square analysis showed no significant difference in bacterial colonization ($P\geq0.05$, 1 df) in the 48-h sputum. Logged colony counts showed higher colony counts on the 48-h suction catheter tips (t test, P=<0.05).

There was no significant difference in the amount of nosocomial colonization between the 24- and 48-h groups. As a consequence there is no need to change these systems routinely at 24 h, therefore minimizing tubing manipulation and reducing revenue costs.

Keywords: infection, bacterial; equipment, breathing system

References

1. Craven DE, Goularte TA, Make BJ. *American Review of Respiratory Disease* 1984; 129: 625–628.
2. Dreyfuss D, Djedaini K. Weber P, Brun P, Lanore JJ, Rahmani J, Boussougant Y, Coste F. *American Review of Respiratory Disease* 1991; 143: 738–743.

The pressure limited tracheal tube cuff: prevention of aspiration of oropharyngeal fluid to the lungs

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Micro-aspiration of oropharyngeal fluid to the lungs past the tracheal tube cuff is a leading cause of ventilator-associated pneumonia (VAP).[1]

A new design of tracheal tube cuff, the pressure limited cuff (PLC),[2] was compared with the Portex Profile high volume low pressure cuff (HVLP), for leakage of dye from the oropharynx to the trachea. The PLC tube is made of latex bonded at stretch to a standard tube so that on inflation within a trachea there are no folds within the cuff walls. Critically the cuff inflation characteristics are such that with a given intracuff pressure, tracheal wall pressure is 30 cm H_2O.

This was a randomized, controlled study. Patients requiring ventilation received either a HVLP or a PLC tracheal tube. A fine catheter (Portex, epidural catheter) was affixed above the cuffs of both types of tube. No lubrication was applied to either cuff. After intubation 0.5 ml of blue food dye was instilled above the cuffs once daily. Routine 4-hourly tracheal suctioning was performed by nursing staff and the tracheal wall pressure for both cuffs was maintained at 30 cm H_2O. This pressure was maintained in the PLC with its inflation device, and in the HVLP cuff by three times daily cuff pressure monitoring. Dye recovered from the trachea within 24 h of instillation was recorded as aspiration.

Forty-six days of ventilation were studied in 12 patients. There were no episodes of aspiration in 35 patient days in the PLC group and eight episodes of aspiration in the 11 patient days in the HVLP group ($P<0.0001$, Fisher's exact test).

This study clearly demonstrated that the new PLC tracheal tube prevented leakage of fluid to the lungs in the intubated and mechanically ventilated intensive care patient. The impact of this on ventilator-associated pneumonia and lung injury has yet to be studied.

Keywords: equipment, tubes tracheal; Intubation tracheal

References

1. Rello J, Torres A. *Seminars in Respiratory Infections* 1996; **11**: 24–31.
2. Young PJ, Ridley SA, Downward G. *British Journal of Anaesthesia* 1998; (in press) (abstract in *Clinical Intensive Care* 1997; 8: 107).

Hypoxic brain injury and neurone specific enolase

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This study was designed to evaluate the possible use of neurone specific enolase (NSE) as a prognostic indicator after hypoxic brain injury. NSE is a cell specific isoform of the enzyme enolase involved in the glycolytic pathway. It is structurally and immunologically distinct from non-neuronal enolases and is found in brain tissue and neuroendocrine cells. When neuronal damage occurs after a hypoxic event, NSE is released.[1] Moderately increased concentrations have been found in patients with non-malignant lung diseases[2] suggesting that there may be a correlation between low oxygen tension in the lungs and release of NSE.

NSE concentrations were measured in serial blood samples obtained from all adult patients referred for intensive care after a clinically significant hypoxic event during a period of 10 months. Trauma patients were excluded. Two methods were used; a radioimmunoassay (Pharmacia) and a fluoroimmunometric assay (Wallac Delphia).

Fifteen patients were studied. There was no significant difference between NSE concentrations obtained by either method. Figure 11 indicates the peak concentration measured in each patient. It was difficult to interpret the results in several patients. Patient No. 10 had no data for the initial 48 h and was also profoundly hypothyroid. Patients Nos 11 and 12 had intercurrent chest infections.[2] Active treatment was withdrawn from patient No. 4 and patient No. 7 died from cardiovascular complications. Patient No. 8 was thought to have a poor prognosis and was not referred for appropriate care, but regained consciousness after 2 days and recovered completely. If NSE concentrations had been known at the time, different decisions might have been made.

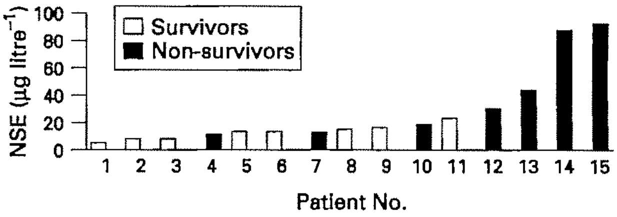

Figure 11 Concentrations of neurone specific enolase (NSE) in survivors and non-survivors.

It is very difficult to give a clear indication of the probable outcome in unconscious patients after a hypoxic episode. In this study, a low NSE concentration appeared to indicate a good prognosis and a high concentration suggested a poor prognosis. Measurement of this enzyme may add valuable additional information in such cases.

Keywords: brain, injury; enzymes, neurone specific enolase

References

1. Dauberscmidt R, Zinsmeyer J, Mrochen H, Meyer M. *Molecular and Chemical Neuropathology* 1991; 14: 237–249.
2. Collazos J, Esteban C, Fernandez A. *Clinical Chemistry* 1994; 40: 266–267.

British Journal of Anaesthesia 1998; **81**: 825–829

CORRESPONDENCE

Complication of the transtracheal catheter

Editor,—We report an unusual complication of a transtracheal catheter used to ventilate the lungs of a patient undergoing fibreoptic intubation.

A 53-yr-old male presented for resection of a carcinoma of the floor of the mouth and reconstruction using a free myocutaneous radial forearm flap. Airway examination revealed limited mouth opening of 1–2 cm but good extension of the neck at the atlanto-axial joint. Nasal fibreoptic intubation was planned with the aid of cricothyrotomy and tracheal jet ventilation to oxygenate the patient's lungs. Following sedation with propofol, 1% lidocaine (lignocaine) was injected first into the skin and then another 2 ml into the trachea through a cricothyroid membrane puncture using a 23-gauge needle.

A 14-gauge transtracheal catheter (VBM-Germany) was inserted in one manoeuvre through the cricothyroid membrane and the introducer withdrawn. Placement in the trachea was confirmed by aspiration of air into a saline-filled syringe, capnography and a small jet of oxygen delivered from a high pressure Sanders injector, which caused the patient to cough. Anaesthesia was induced with propofol and fentanyl, and neuromuscular block was achieved with vecuronium. Commencement of assisted ventilation using the injector caused immediate swelling with crepitus around the catheter site, extending down the anterior aspect of the patient's neck. The catheter was removed immediately, ventilation via a face mask was confirmed and fibreoptic intubation performed with oxygen insufflation and apnoea. No complications appeared as a result of surgical emphysema, and the operative procedure, including a modified radical supraomohyoid neck dissection, was uneventful.

Subsequent inspection of the catheter demonstrated laceration at the junction of the catheter sheath and hub (fig. 1). This had allowed oxygen to be forced into the paratracheal tissues despite correct placement of the catheter tip into the tracheal lumen. The mechanism by which this hole was made is unknown. It may have occurred at manufacture, although neither the manufacturer nor the suppliers of this transtracheal catheter have received a similar report. The introducer needle has a preformed curve and a 30° bevel tip. Although at no time was the needle reintroduced into the catheter, it is more likely that this perforation occurred at placement. It is possible that when withdrawing the needle any rotation within the plastic catheter could result in a similar cut, although we have found this difficult to reproduce *in vitro*.

We have found that elective use of a transtracheal catheter to aid fibreoptic intubation is highly acceptable. It is of value in patients who will not tolerate topical or awake nasotracheal intubation, particularly young children, the mentally handicapped and patients for whom communication is difficult.[1] Increasingly, at this hospital it is the preferred technique for all patients with a difficult airway requiring intubation, provided that they have reasonable neck extension and a palpable cricothyroid membrane. By leaving the catheter in position after operation, there is an immediately available means of ventilation should airway difficulty occur after extubation.[2] It has a low morbidity that appears primarily related to tissue emphysema through displacement of the catheter.[3] However, barotrauma with resultant pneumothorax has been reported, as has oesophageal puncture, bleeding and haemoptysis.[3]

Whatever the mechanism of action that caused the perforation, this complication could have had serious consequences. This case highlights the need for constant vigilance when using an oxygen injector via a transtracheal catheter for intermittent positive pressure ventilation of the lungs.

W. Ames
P. Venn

1. Barham CJ. Anaesthesia for maxillofacial surgery. In: Patel H. *Anaesthesia for Burns, Maxillofacial and Plastic Surgery*. London: Edward Arnold, 1993; 53–77.
2. Benumof JL, Scheller MS. The importance of transtracheal jet ventilation in the management of the difficult airway. *Anesthesiology* 1989; 71: 769–778.
3. McLellan I, Gordon P, Khawaja S, Thomas A. Percutaneous transtracheal high frequency jet ventilation as an aid to difficult intubation. *Canadian Journal of Anaesthesia* 1988; 35: 404–405.

Blood transfusion for Caesarean section

Editor,—We read with interest the article by Rainaldi and colleagues[1] describing the use of blood salvage during Caesarean section. We were surprised that 23.5% of women in the control group required blood transfusion after operation. As a result, we conducted a survey into the use of blood products in maternity patients in our hospital. During 1997, 642 Caesarean sections were performed, of which 32 (4.98%) received blood transfusions in the period between the day of operation and day of discharge. Table 1 shows the indication and timing of transfusion in our patients.

This major difference in transfusion rate between our patients and those in the study is surprising. Unfortunately, no details are provided on the indications for administration of blood, estimated

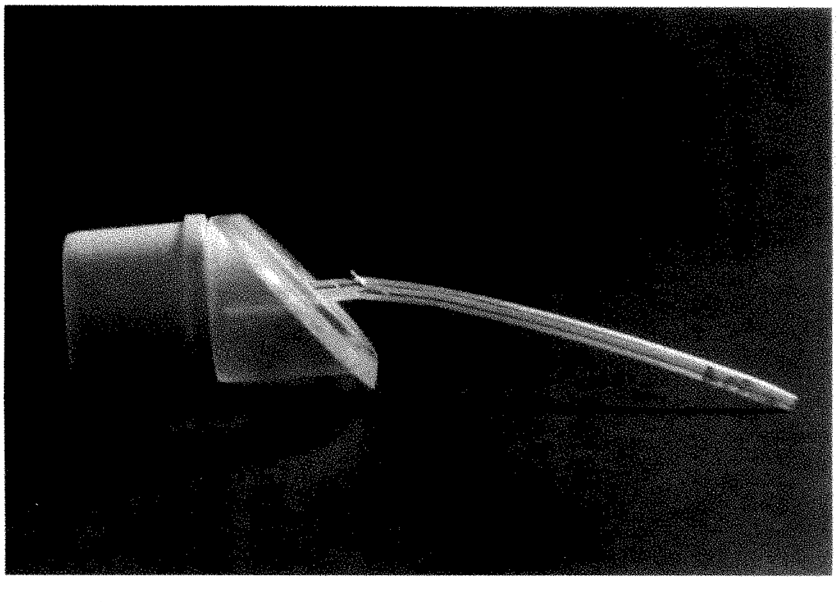

Figure 1 Photograph of the transtracheal catheter, showing the laceration at the junction of the catheter sheath and hub.

Table 1 Timing, indication and incidence of blood transfusion associated with Caesarean section

Time of transfusion	Indication	No. of patients
Intraoperative	Preoperative anaemia	5
	Blood loss	4
Postoperative	Anaemia and/or intraoperative blood loss	13
	Post-partum haemorrhage	10

Table 2 Factors which may be associated with excess bleeding during Caesarean section in the two groups

Factor	Blood salvage	No blood salvage
Repeat Caesarean section	14	9
Multiple pregnancy	7	1
Placenta praevia	3	1
(Fibroids	5	0)
(Coagulopathy	2	0)

operative blood loss or the use of oxytocic agents. Further, there appears to be a greater proportion of patients with conditions normally associated with increased intraoperative blood loss in the group that underwent blood salvage (table 2).

Although these patients would be at a greater risk of postoperative anaemia, it could equally be argued that excessive intraoperative bleeding would contribute to the volume of blood successfully salvaged. However, even with the increased risk of intraoperative haemorrhage, the average volume of red blood cells salvaged was equivalent to only 1.5 u. of packed cells. We have to assume that all of the salvaged blood was reinfused.

We feel that the high transfusion rate in the control group can be explained in two ways. Either patients experienced a greater operative blood loss or the authors transfused patients who were only mildly anaemic. Although the technique of blood salvage during Caesarean section may be safe, we would conclude that it would be of most benefit to patients with placental abruption or placenta accreta, when large volumes of blood could be salvaged. As these events tend to be rare and unpredictable, the beneficial use of blood salvage during Caesarean section will be limited.

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1. Rainaldi MP, Tazzari PL, Scagliarini G, Borghi B, Conte R. Blood salvage during Caesarean section. *British Journal of Anaesthesia* 1998; **80**: 195–198.

Editor,—Our study was not concerned with the assessment of bleeding or any adverse reaction to the use of oxytocics, surgical techniques, etc. We wanted to assess the clinical and laboratory results in the patients studied. It must be pointed out that there are a large number of cases admitted to the university clinic with "at risk" pregnancies (tables 1, 2). The clinic is also home to the postgraduate school of obstetrics and gynaecology. A protocol was devised for the use of intraoperatively salvaged blood in Caesarean section. The effects on haemoglobin concentration and length of time the patient stayed in hospital were evaluated, because a link was found between long hospital stay and anaemia, which was not corrected by homologous blood transfusion. The transfusion of packed red cells was carried out only when the patient could not tolerate the anaemia. The cost of the kit used to salvage blood was less then 1 day's stay in hospital!

I appreciate the low incidence of homologous transfusions in Stockport and note their ability to predict intraoperative bleeding. The mean intraoperative salvage in our study was 363 ml (range 125–800 ml). In eight cases (23.5) the amount of intraoperative blood salvage was equal to or more than 500 ml. I think that without intraoperative salvage these patients would have needed homologous transfusions and probably a longer stay in hospital.

Studies are underway to verify if this 68 patient report reflects routine clinical experience and if it is necessary to adopt guidelines to restrict or extend indications for blood salvage.

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Postoperative hypoxaemia

Editor,—I was surprised to read from Motamed and colleagues that continuous epidural analgesia resulted in more episodes of desaturation during the postoperative period than patient-controlled analgesia until I appreciated that morphine was being used in the epidural mixture together with bupivacaine.[1] Morphine is a very water-soluble opioid and has been recognized for several years to be unpredictable in its respiratory depressant effect. I would caution readers to extrapolate from this article the idea that all epidural opioid–local anaesthetic mixtures are dangerous. The use of weak bupivacaine solutions (0.1–0.15%) with fentanyl 2–4 μg ml^{-1} produces a safe, synergistic effect with minimal motor block and respiratory depression.

I would be grateful for clarification as to whether the amount of morphine delivered in the study was 0.25 mg h^{-1} (as written in the summary) or 0.25 ml ml^{-1} (as written in the methodology).

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1. Motamed C, Spencer A, Farhat F, Bourgain JL, Lasser P, Jayr C. Postoperative hypoxaemia: continuous extradural infusion of bupivacaine and morphine *vs* patient-controlled analgesia with i.v. morphine. *British Journal of Anaesthesia* 1998; **80**: 742–747.

Editor,—We are grateful to Dr Stuart-Taylor for her careful reading of our article.[1] We agree that continuous epidural analgesia with a combination of local anaesthetic and opioid carries a risk of late respiratory depression as a result of systemic or CSF absorption of the opioid.[2 3] However, opioids provide sustained pain relief[4 5] and although the incidence of late respiratory depression is low (0.09–0.2%), it may occur with hydrosoluble or liposoluble opioids.[2 3 7] Several studies have evaluated the occurrence of desaturation after different types of analgesia, finding that hypoxaemia occurred in all analgesia groups, although epidural analgesia tended to cause longer periods of desaturation.[8]

Many surveys have reported that epidural analgesia using either opioids alone or a combination of local anaesthetics and opioids is safe in the ward provided that adequate nursing monitoring is available.[2 3 7 9] This regimen can be used without sophisticated monitoring techniques.[10 11] The risk of respiratory depression or hypoxaemia, or both, after epidural opioid analgesia can be minimized by oxygen treatment. Standing orders for patients receiving epidural opioids include avoidance of parenteral opioids. Although epidural analgesia is associated with longer episodes of hypoxaemia, it produces better pain relief which may result in more rapid patient mobilization with potentially fewer postoperative complications.[10]

We apologize for the mistake in the methodology section; the correct dose of morphine is 0.25 mg h^{-1}, the dilution of the mixture infused in the epidural space is 0.125% bupivacaine associated with morphine 0.025 mg ml^{-1}, and the rate of infusion is 10 ml h^{-1}.

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1. Motamed C, Spencer A, Farhat F, Bourgain JL, Lasser P, Jayr C. Postoperative hypoxaemia: continuous extradural infusion of bupivacaine and morphine *vs* patient-controlled analgesia with i.v. morphine. *British Journal of Anaesthesia* 1998; **80**: 742–747.
2. Broekema AA, Gielen MJM, Hennis PJ. Postoperative analgesia with continuous epidural sufentanil and bupivacaine: A prospective study in 614 patients. *Anesthesia and Analgesia* 1996; **82**: 754–759.
3. Scott DA, Beilby DS, McClymont C. Postoperative analgesia

using epidural infusions of fentanyl with bupivacaine. *Anesthesiology* 1995; **83**: 727–737.

4. Mitchell RWD, Scott DB, Holmquist E, Lamont M. Continuous extradural infusion of 0.125% bupivacaine for pain relief after lower abdominal surgery. *British Journal of Anaesthesia* 1988; **60**: 851–853.
5. Shafer AL, Donnelly A. Management of postoperative pain by continuous epidural infusion of analgesics. *Clinical Pharmacology* 1991; **10**: 745–765.
6. Lee A, Simpson A, Whitefield A, Scott DB. Postoperative analgesia by continuous extradural infusion of bupivacaine and morphine. *British Journal of Anaesthesia* 1988; **60**: 845–850.
7. Schug AS, Torrie JJ. Safety assessment of postoperative pain management by an acute pain service. *Pain* 1993; **55**: 387–391.
8. Madej TH, Wheatley RG, Jackson IJB, Hunter D. Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient controlled analgesia. *British Journal of Anaesthesia* 1992; **69**. 554–557.
9. Ready BL, Oden R, Chadwick HS, Benedetti C, Rooke GA, Caplan R, Wild LM. Development of an anesthesiology-based postoperative pain management service. *Anesthesiology* 1988; **68**: 100–106.
10. Liu S, Carpenter RL, Neal J. Epidural anesthesia and analgesia, their role in postoperative outcome. *Anesthesiology* 1995; **82**: 1474–1506.
11. Jayr C, Thomas H, Rey A, Farhat F, Lasser PH, Bourgain JL. Postoperative pulmonary complication. Epidural analgesia using bupivacaine and opioids versus parenteral opioids. *Anesthesiology* 1993; **78**: 666–676.

Accidental i.v. injection of local anaesthetic

Editor,—We agree with Checketts and Wildsmith that negative aspiration, test dosing and slow administration of divided doses of local anaesthetic are important steps in preventing complications relating to epidural catheter misplacement.[1] However, the report by Abouleish, Elias and Nelson demonstrated that, despite these measures, systemic toxicity after inadvertent i.v. injection may still occur. We would like to describe one additional precautionary test that may have prevented systemic toxicity in this case.

After negative aspiration, it is our practice to ask patients to describe what is felt during the subsequent epidural injection. A sensation of cold is invariably felt in the patient's back after administering 2–3 ml of local anaesthetic. It can be diffuse or localized. The commonest site is the mid thoracic region but it may be felt at any point along the vertebral column. It is experienced not only during the initial test dose, but also with each subsequent injection. This sensation is most likely a result of spread of fluid within the epidural space and therefore may not be felt if accidental i.v. or intrathecal injection occurs. We feel that seeking this sensation after injecting a small volume of local anaesthetic is a useful additional safety measure when trying to confirm correct epidural catheter placement and certainly merits further investigation.

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1. Checketts MR, Wildsmith JAW. Accidental i.v. injection of local anaesthetics: an avoidable event? *British Journal of Anaesthesia* 1998; **80**: 710–711.
2. Abouleish EI, Elias M, Nelson C. Ropivacaine-induced seizure following extradural anaesthesia: a case report. *British Journal of Anaesthesia* 1998; **80**: 843–844.

Editor,—The editorial by Checketts and Wildsmith[1] discussed the usefulness of test dosing to detect i.v. epidural catheter placement. The fact that neither a test dose nor aspirating the epidural catheter can guarantee i.v. misplacement of the catheter is well illustrated by the accompanying case report.[2] However, the sensitivity of the "aspiration" test may be improved by using a technique similar to that described by Shah.[3]

Having inserted an epidural catheter and flushed it with saline, it is my routine practice to remove the filter and elevate the end of the catheter 20–30 cm above the level of insertion to confirm a falling meniscus that fluctuates with respiration. The open-ended catheter is then lowered to a similar distance *below* the site of insertion, to detect excessive flow of clear fluid (which may be tested for glucose if intrathecal placement is suspected) or the appearance of blood. It is my experience that blood may appear in the catheter under these circumstances, when none has been evident on aspirating with a syringe. Presumably, generation of an excessively negative pressure at the catheter tip when aspirating with a syringe collapses the epidural vein and so blocks the catheter holes rather than permitting aspiration of blood. Conversely, lowering the open-ended catheter allows blood to flow down a gentle pressure gradient and appear in the catheter. Depending on the epidural venous pressure and the length of the catheter inserted, this may take a few seconds. Failure of any flow of saline at this stage may also indicate malposition of the catheter tip, for example lodgement in an intervertebral foramen. Cautious withdrawal until flow occurs is a further assurance of correct catheter placement. Finally, the catheter should be visible at or very near its point of insertion—using non-transparent dressings over the epidural site hinders detection of blood in the catheter.

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1. Checketts MR, Wildsmith JAW. Accidental i.v. injection of local anaesthetics: an avoidable event? *British Journal of Anaesthesia* 1998; **80**: 710–711.
2. Abouleish EI, Elias M, Nelson C. Ropivicaine-induced seizure following extradural anaesthesia. *British Journal of Anaesthesia* 1998; **80**: 843–844.
3. Shah JL. A test to show correct placement of epidural catheter. *Anaesthesia* 1982; **37**: 426–427.

Editor,—We read the case report[1] regarding this unpleasant and potentially dangerous complication of extradural anaesthesia, and the accompanying editorial[2] with interest. While fractionating of the main dose remains the optimum method of avoiding a serious reaction if the dose was systemic,[3] perhaps there are other lessons to be learnt from this report. Although the authors have stated that there were no signs of subarachnoid block after administration of ropivacaine 45 mg, they state later in the same paragraph that no sensory or motor effects were seen after a total dose of 120 mg. The complete absence of any block after the first three fractions could have been an indication that the catheter was misplaced which prevented the fourth and fifth fractions from being given. The effect of ropivacaine 75 mg (the first three doses) (1.27 mg kg^{-1}) should have produced early signs of sensory block such as warmth or tingling, despite the slow onset of plain ropivacaine.[4] We recommend that we should elicit the lack of epidural anaesthesia with as much vigour as looking for signs and symptoms of systemic toxicity.

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A. Marchant
University Hospital of Wales

1. Abouleish EI, Elias M, Nelson C. Ropivacaine-induced seizure after extradural anaesthesia. *British Journal of Anaesthesia* 1998; **80**: 843–844.
2. Checketts MR, Wildsmith JAW. Accidental i.v. injection of local anaesthetics: an avoidable error? *British Journal of Anaesthesia* 1998; **80**: 710–711.
3. Scott DB. Test doses in extradural block. *British Journal of Anaesthesia* 1988; **61**: 129–130.
4. Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. *British Journal of Anaesthesia* 1991, **66**: 31–37.

Editor,—We thank your correspondents for their interest in our editorial, and you for the opportunity to comment further. Before responding specifically to their individual points we feel it is important to repeat the major message:

(1) There is currently no practical method of physically demonstrating *with absolute certainty* that an epidural catheter does or does not lie within a vein.

(2) Any putative test dose must have a high probability of producing systemic effects without causing harm.

(3) Any significant dose of local anaesthetic agent must be injected incrementally.

Discussion of detailed points of technique must not be allowed to obscure these vital aspects. We all have our favoured "tricks of the trade", but none provide immunity from a major reaction, the (fortunately) low incidence of which means that it may take a long time for a false premise to be revealed clinically.

Bowler and Marchant suggest that the complete absence of signs of block after 75 mg of ropivacaine had been injected via the epidural catheter of the patient reported by Abouleish, Elias and Nelson[1] should have caused concern. However, the mean time to pinprick block of L1 after 75 mg (15 ml of 0 5%) of epidural ropivacaine in the study quoted was 8 min, and less than 50% of the patients achieved a Bromage grade 1 motor block at any time.[2] Some patience is therefore required. In addition, we are aware of a patient developing ventricular fibrillation after accidental i.v. injection of as little as 50 mg (10 ml of 0.5%) of bupivacaine, albeit very rapidly. Thus unless administered as a very slow injection, the i.v. toxic dose is almost certainly less than the effective dose. Finally, sensations of warmth and paraesthesiae are not always reported by patients and therefore are not reliable markers of correct placement of an epidural catheter. Indeed they may be described after i.v. injection!

McAtamney, Connolly and Carabine stated that a cold sensation is felt in the patient's back during epidural injection. We have never had a patient remark on this sensation and it is incautious of them to describe it as "a useful additional safety measure" when they also suggest it "merits further investigation".

Woodward's suggestion of using Shah's[3] technique to confirm correct epidural catheter placement is not new and has its advocates, including us. However, this method has not been shown to be any better at detecting epidural vein cannulation than a *gentle* aspiration test with a 2-ml syringe (which itself is not infallible as we have seen) although we use both aspiration and syphon tests in the hope of identifying i.v. placement sooner rather than later.

M. R. CHECKETTS
J. A. W. WILDSMITH
University of Dundee
Dundee

1. Abouleish EI, Elias M, Nelson C. Ropivacaine-induced seizure after extradural anaesthesia. *British Journal of Anaesthesia* 1998; 80: 843–844.
2. Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JA. Comparison of extradural ropivacaine and bupivacaine. *British Journal of Anaesthesia* 1991; 66: 31–37.
3. Shah JL. A test to show correct placement of epidural catheter. *Anaesthesia* 1982; 37: 426–427.

Editor,—We read with interest Dr Woodward's letter. One of the points he raised is that negative aspiration of blood can result from occlusion of the tip of the catheter by the wall of the blood vessel, as a result of creation of negative pressure on aspiration. We not only agree with his statement, but also practice and teach it. Dr Abouleish, in his book entitled "Pain control in obstetrics" published 21 yr ago,[1] stated "A catheter can be in a blood vessel and yet no blood is aspirated because the tip can be against the vessel wall. In such a case, aspiration following injection of 2 ml of solution is more liable to obtain a sanguineous aspiration than prior to injection, because the injectate distends the vein and separates the catheter tip from the vessel wall. However, as mentioned before, aspiration can be negative even if the catheter tip lies in a blood vessel. Therefore, aspiration is only important when positive and the only reliable sign that the catheter is inside a blood vessel is the reaction of the patient to the test dose." In our case report, aspiration was negative before and after injection of the local anaesthetic. We also agree with Dr Woodward that a transparent tape is advisable, and we mentioned that in the discussion of the article. Moreover, when aspiration is performed with the patient on her side, the point of insertion is easily seen and blood in the catheter is detected early.

To stay within the allotted space for the article, we did not discuss many aspects of test doses and intravascular malposition of an epidural catheter. We think the editorial by Drs Checketts and Wildsmith is excellent. It expanded the discussion and shed light on these controversies.[2]

In summary, the purposes of our article were to alert anaesthetists that all local anaesthetics are potentially toxic, to demonstrate the relative safety of ropivacaine and to emphasize that vigilance, a high index of suspicion, and fractionation of the therapeutic dose are the main factors to prevent *cardiac* toxicity from local anaesthetics.

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1. Abouleish E. *Pain Control in Obstetrics.* Philadelphia: JB Lippincott 1977; 244–245.
2. Checketts MR, Wildsmith JAW. Accidental i.v. injection of local anaesthetics: an avoidable event? *British Journal of Anaesthesia* 1998; 80: 710–711.

ERRATUM

A guide for tube exchange using a fibrescope and the plastic sheath of a guidewire in small children (BJA 1998; 81: 103)
The name of Dr J. -H. Bahk was spelt incorrectly in his letter to the editor.
We apologize to the author for this error, which arose during the editorial process.

British Journal of Anaesthesia 1998; **81**: 829–833

BOOK REVIEWS

Obstetric Anesthesia and Uncommon Disorders. D. R. GAMBLING AND M. J. DOUGLAS. Published by W. B. Saunders, Philadelphia. Pp. 463; indexed; illustrated.

Advances in the medical (and surgical) treatment of many disorders have meant that more women are reaching child-bearing age and becoming pregnant. This has inevitably brought new challenges to the obstetric anaesthetist who needs to know the effect of the physiological changes of pregnancy on a wide range of pathological processes. Although textbooks are available which cover the anaesthetic implications of uncommon medical disorders, until now there has been none which emphasizes the impact of the disorder on pregnancy, the impact of pregnancy on the disorder and the effect of therapy for the disorder on the fetus and neonate.

The book is organized on a systems basis and draws together case reports and experience from the world literature. I looked at the information given on relatively unusual disorders (cardiomyopathy; mitral regurgitation; Fontan's operation for a single ventricle; Ehler's Danlos syndrome) which we have recently encountered in our hospital, and found it enormously helpful. Not only are there concise, relevant descriptions of the problem and anaesthetic management, but the original articles and case reports are also well referenced for easy access. Is the book comprehensive? It appears to be, covering conditions as diverse as cystic fibrosis, acute severe asthma, rheumatoid arthritis and transplants (heart, heart–lung, liver, kidney and pancreas–kidney). Inevitably, people will come across a condition not mentioned—they will then realize that they need to publish their experience with that disorder!

The authors rightly point out that the obstetric anaesthetist is often asked at short notice to provide care for parturients with unusual conditions, at a time (e.g. the middle of the night) when it is difficult to access the appropriate case reports. This book enables the appropriate care to be given with the benefit of published experience. I wholeheartedly recommend this book. It is a must for every delivery suite!

G. M. Cooper

Drugs, Diseases, and Anesthesia. STERN. ISBN: 0-397-58758-9 (five PC compatible 3½" disks); 0-397-58764-3 (five PC compatible 3½" disks, Network Version). Price US $99.00 (US $395.00 Network Version).

This piece of software was supplied well packaged with adequate installation instructions. The version supplied was for an IBM-compatible PC running either Windows 3.X or 95. It was supplied on five 3½ inch high-density disks which were virus-free and took less than 5 min to install. It is actually a group of databases, with their linking and display modules running under Paradox for Windows. In the event of problems, the instructions describe technical support but it is only available in office hours US Pacific Standard time (GMT minus 8 h).

The information on the packaging describes "200 patient–drug–anaesthetic interactions, 60 disease–anaesthetic interactions and 100 anaesthetic–anaesthetic interactions". Therefore, it contains a great deal of information but does not cover every eventuality. Those encountered most commonly in clinical anaesthetic practice are present.

Double-click on the appropriate icon and the operator is presented with a window containing the main screen. Three small windows arranged horizontally are entitled patient drugs, diseases and anaesthetics, and in each is a scrollable list. A large full-width window below displays information concerning the selection made in any one of the three top windows. The operator can select either the generic name or the brand name for the drugs using check-boxes, and a button is supplied to print the advice given. Selecting the button labelled "See interactions with ..." does exactly what it says. A double click on any entry in one of the three small windows does the same. A second full size window appears which looks almost identical to the main screen but is labelled "Interactions with...". Selecting any entry from the three small windows on this new screen gives information on interactions with whatever was originally chosen.

I found the package easy to use. The information and advice is sensible and straightforward and not verbose, but may be over-brief in some places. It tells the reader the important points, appropriately arranged under sub-headings (e.g. classification, indications, pharmacology, interactions and relevance to anaesthesia). It is specific for anaesthetic practice and thus of interest to all anaesthetists. There are a few difficulties. The first and major problem is that it is written with an American audience in mind. As such, all of the drug spellings are in US format and brand (trade) names are US names. Many are the same but the differences are sufficient to produce a problem. There are also drugs available in the US which are not available in the UK (e.g. sufentanil, doxacurium) and formulation differences (e.g. amiodarone is stated to be available only orally yet there is an i.v. preparation in the UK) Some drugs have totally different names (e.g. meperidine is listed yet pethidine is not). One irritating quirk of the program is that when scanning down one of the three small primary windows, the bottom entry on the list appears high-lighted but the information window still contains the entry for the previously selected choice It is necessary to click again on the high-lighted entry to change the information window. There are some surprises within the principal lists. For example, I was interested to see that advanced age is a disease and also that chlordiazepoxide is an anaesthetic drug.

It is clear that a great deal of work has gone into preparing the data and links within this piece of software. I suspect that it will not be a best-seller in the UK or in Europe because of the strong US bias. It is, however, a piece of software which contains a great deal of information and I feel marks the beginning of a direction in which we will eventually be progressing I look forward to seeing more software in this mould in the future. Have the authors considered producing a version aimed at the UK and Europe markets?

B. J. Pollard

Sickle Cell Pain. Progress in Pain Research and Management, Vol. 11. S. K. BALLAS. Published by IASP Press, Seattle Pp. 379; indexed; illustrated. Price £87.

This book is one of a series of publications by the International Association for the Study of Pain, produced with the intention of providing low-cost books on this topic, although whether £87 can be described as low cost is arguable.

Sickle cell disease (SCD) is a formidable clinical problem. It is a disease of patients from one racial group, where racial and political overtones have led to considerable conflict with health care providers. In his introduction, the author describes a recent demand by activists that sufferers be called not patients with SCD but "sickle cell defiers". This monograph is a very personal and at times almost passionate call for better management of this distressing disease. Any book that concludes with a section entitled "Lack of awareness in the ivory tower", a rather bitter response to a rejection of one of the author's papers, is obviously not a dry medical text.

The book is divided into five main sections, the first two dealing with the clinical and pathological features of SCD, and the remainder with the management of acute and chronic pain syndromes associated with it. The text is interspersed with brief clinical vignettes and short discussions. I found the chapter on genetics and pathology rather confusing, with a considerable amount of space devoted to comparisons with other haemoglobinopathies. I expect this reflects the author's background as a haematologist leading him to make assumptions about the level of knowledge of the general reader. Despite being primarily concerned with pain, the book also covers the clinical features of SCD and other medical emergencies such as the "acute chest crisis". The chapters on pain management are excellent.

Although a haematologist, Dr Ballas undoubtedly talks the language with which any anaesthetist would instantly feel at home. For this reason it is rather disappointing that he makes no reference to anaesthetists and their expertise in pain management. Despite extensive discussion of techniques such as PCA and opioid infusions, there are virtually no references from anaesthetic sources. This presumably reflects US medical practice where the majority of patients with SCD are treated in specialist centres which have more than 500 patients on their books and who are managed exclusively by haematologists. The section on analgesic pharmacology is excellent, as are the sections dealing with non-pharmacological and new methods of treatment. Dr Ballas is a firm believer in the use of strong analgesics in the management of a crisis, and argues forcefully for them. His frustration at the attitude of some of the medical establishment to opioid prescribing for SCD is forcibly expressed throughout the text. He cautions against the use of data proposing more modest use of opioids, pointing out that patients will "hospital shop" until they get adequate analgesia. Alternative therapies, hydroxyurea and bone marrow transplantation are given extensive coverage. Every section is referenced.

There are problems for the European reader as the book is aimed at a US audience and as such does not mention diamorphine, referring extensively to oxymorphone and hydromorphone; discussion of other analgesics is also notable for considerable transatlantic differences. The author tends to stress respiratory rate rather than sedation scores in the prevention of opioid-induced respiratory depression, when it is now known that the latter is probably more important.

My criticisms are minor. This book appears to be based on extensive practical experience with realistic observations on the therapeutic modalities available, backed up by a comprehensive review of the literature. The author does not shy away from the difficult issues surrounding the management of SCD pain. I think the book is ideal for any doctor who is likely to have significant exposure to patients with SCD whether they are haematologists, accident and emergency staff or specialist anaesthetists. As a monograph it makes a good read and should be viewed as such, rather than as a reference text. With a bit of luck it might lead to better and more generous prescribing for patients with SCD.

P. M. Yate

An Evidence-based Resource for Pain Relief. H. J. McQuay and R. A. Moore. Published by Oxford University Press, Oxford. Pp. 264; indexed. Price £65.00

This book sets out to provide not the answer to the question "which analgesic or analgesic method" but rather to offer ways in which accurate assessments of the available clinical data can be made to act as a guide to answering that problematic question. The authors wish the book to offer an explicit approach to this assessment of evidence and, provided one accepts the inevitable limitations, it has succeeded.

The volume is divided into three parts dealing with methodology, treatments of acute pain and chronic pain. Each part in itself is an education and could stand alone, but together the resultant book is impressive.

The first part is based on the premise that evidence of treatment adequacy which is both relevant and valid is necessary for effective care. The randomized, controlled study is the most reliable method of estimating the effect of an intervention. There follows details of how to approach that estimation and to measure the strength of that finding. The second and third parts of the book detail systematic reviews of randomized, controlled studies with a variety of analgesic substances and techniques in the treatment of postoperative, obstetric and chronic pain situations. It is by no means a complete list and the reader will search in vain for the use of i.v. or i.m. injections of analgesics and other pain relieving techniques. Nevertheless, the amount of information is prodigious and the conclusions drawn will give much food for thought and, one hopes, eventual changes in clinical practice.

The book has 257 pages and a comprehensive index, and discusses 23 different studies. The reference lists are as comprehensive as one would wish and point the way to further study of value. As the authors state, this book is not the final word. One would hope not, as to peruse this volume is to be left thirsting for more, and one trusts that this will be forthcoming in the not too far distant future.

This book should be purchased by all who have any interest in pain and its treatment. It should be statutory reading for all who teach and learn, notwithstanding those who seek to venture into the research area. It acts as a salutary lesson to us all. It is also comforting that the authors have space to remember their mentors, especially John Lloyd, who started them on this valuable road. Long may they continue to produce such informative and stimulating material.

It is a long time since this reviewer came upon a book that generated such enthusiasm. Usually niggardly with praise, this volume engendered plaudits galore; I trust you will find it as excellent as I have.

K. Budd

The Pathophysiology of Pneumoperitoneum. R. J. Rosenthal, R. L. Friedman and E. H. Phillips. Published by Springer-Verlag, Berlin. Pp. 187; illustrated. Price £57.00.

Drs Rosenthal, Friedman and Phillips from Mount Sinai/Beth Israel Medical Centers, New York and Cedar Sinai Medical Center, Los Angeles, have compiled a comprehensive monograph on the pathophysiology of pneumoperitoneum for laparoscopic surgery.

Pneumoperitoneum, usually obtained by intraperitoneal insufflation of carbon dioxide, provides the visceral separation required for most laparoscopic procedures. This 187-page monograph begins with a historical review of milestones in the evolution of laparoscopic surgery. For the most part, gynaecologists developed the instrumentation, operating principles and techniques for operative laparoscopy. The apparent lack of attention given to laparoscopy by general surgeons, since its development in the early part of the century, was largely a result of its perceived role as a diagnostic rather than therapeutic tool

The advent of laparoscopic cholecystectomy was the catalyst that aroused the interest of general surgeons worldwide in laparoscopy and closed abdominal surgery. The scope of minimal access abdominal, thoracic and pelvic surgery has been extended greatly and new laparoscopic techniques have been developed, performed and advocated for older patients who may have co-existing cardiac and/or pulmonary disease. These laparoscopic procedures may involve reverse Trendelenburg patient position and require a longer period of intraperitoneal carbon dioxide insufflation than the less physiologically disturbing gynaecological procedures. Hence the interest in this timely comprehensive review of the pathophysiological consequences of pneumoperitoneam with assessment of experimental data and the results of clinical studies.

The authors have recruited established authors in the field and the text reflects not only North American but also European and Australian teaching and clinical experience. The text is set out in 16 chapters, ranging from the history of pneumoperitoneum and the effects of intraperitoneal insufflation of carbon dioxide on temperature, hepatoportal–renal–mesenteric blood flow and cardiovascular–respiratory function. Subsequent chapters detail the neuroendocrine responses to laparoscopy and elevation of abdominal pressure, and the complications following trocar insertion and carbon dioxide insufflation. The concluding chapters detail the effects of pneumoperitoneum in paediatric patients and during pregnancy.

As might be expected with contributions from a large number of authors in diverse institutions, there is significant repetition of data relating to the cardiovascular and respiratory effects of pneumoperitoneum and intraoperative complications. Overlap of information is most obvious in chapters 8, 9 and 10. The authors showed some imagination by inviting contributions detailing alternative gases, other than carbon dioxide, and the subsequent changes in body temperature. Hypothermia should be anticipated if laparoscopic procedures are prolonged, especially during oesophageal gastric, colonic or pancreatic resections. Drs Bessel and Maddern suggest that appropriate heat conservation prophylaxis should be instituted in long duration laparoscopic procedures. However, currently available gas warming insufflators have not yet achieved acceptable standards of electrical safety and sterility for clinical use. While it may be unfair to single out one chapter, Dr Lowham and colleagues' contribution (Pneumoperitoneum—related complications: diagnosis and treatment) best captures the essence of problems relating to this topic. Further, the potential for intraoperative venous stasis associated with increased intra-abdominal pressure and reverse Trendelenburg position is highlighted.

Presentation of the text is impressive with division of chapters into introduction, physiological effects, data from experimental and clinical studies, summary and conclusion sections. Special mention should be made of the extensive use of algorithms throughout the text which compliment the data presented and facilitate retention of information.

This timely monograph may be of limited appeal to clinicians for personal purchase. However, it will prove a valuable addition to institutional and anaesthesia/surgery/endoscopy departmental libraries.

M. Harnett
A. J. Cunningham

Handbook of Clinical Anesthesia, 3rd Edn. P. G. Barash, B. F. Cullen and R. K. Stoelting (editors). Published by Lippincott-Raven, Philadelphia. Pp. 993; indexed; illustrated. Price £46.00.

This is a pocket-sized, condensed version of the larger *Clinical Anesthesia* written by the same editors It aims to provide "rapid acquisition and comprehensive understanding of the scientific and clinical foundations of" anaesthesia. The initial impression is that it does provide a useful and highly portable reference text that allows both trainee and established anaesthetists to confirm important data. It also contains enough general information, both clinical and scientific, to enable users to check up on uncommon conditions and their effect on anaesthesia, and to provide an *aide-memoir* for areas of anaesthesia beyond their current working practice.

The previous editions of this book have become established favourites of trainees, taking the place held by the "synopsis" because of their combination of size and comprehensiveness. The keystone of such a book lies in the completeness and accessibility of the indexing. Cross-referencing is almost entirely to the larger sister textbook and therefore the reader may miss salient associations. The main index is full and clear, and this offsets the disadvantage of the cross-referencing if one has already a broad appreciation of the topic areas. Searching at random for selected topics (malignant hyperthermia, Horner's syndrome, hyperkalaemia, ion-selective membrane pores, sleep apnoea and alcohol) was interesting, with no sign of the medical uses or abuses of alcohol, even in the chapter on liver disease.

The clear tables were a very useful guide and summarized key information in a focused manner allowing the reader to use the book when time was pressing. The use of clinical guidelines is less common outside the USA, but again they provide an appropriate response to complex clinical situations. However, non-USA trainees may find the protocols for resuscitation in the appendix very unwieldy. They are too complex for the size of the page, cross from one page to another, and do not clearly conform to the European Resuscitation Guidelines.

There was only one persistent irritation, and that was the binding. The book arrived looking as though it has been through hard times, and I have no doubt that time will not improve it. I wonder if a more rigid plastic cover would not have improved its utility and ruggedness.

Would I buy it? Undoubtedly yes, and I would recommend it to my trainees. I would add that it provides them with rapid access to what they have read elsewhere, but forgotten, rather than as a definitive, exhaustive text—indeed it is exactly as the editors planned it.

C. Dodds

Progress in Pain Research and Management, Vol. 9, Molecular Neurobiology of Pain. D. BORSOOK (editor). Published by IASP Press, Seattle. Pp. 369; indexed; illustrated. Price US$76.00.

Since the cloning of the opioid receptors in 1992, there has been an explosion in publications involving opioids and pain. This volume is a useful addition to this vast literature base. The cloning of the opioid receptors is mentioned throughout the book, indicating the impact that this event has had on researchers in the field.

This edited *International Association for the Study of Pain* volume results from a meeting sponsored by the Massachusetts General Hospital and Harvard Medical School on "Molecular Aspects of the Neurobiology of Pain". There are 18 chapters in total, divided into five sections: developmental aspects of sensory neurones; neurobiology of inflammation; neurobiology of nerve injury; neurobiology of receptor–ion channels involved in pain transmission; and molecular aspects of the future. The authorship (56 in all) is truly international and there are many "household" names in the pain–opioid field. The individual chapters vary in length from just five to 30 pages.

It is perhaps a little unfair to pick out specific chapters as the majority were well written, easy to follow, appropriately illustrated (i.e. a mix of both original data and schemas) and in the main referenced extensively. However, I particularly enjoyed reading sections III (Neurobiology of nerve injury) and IV (Neurobiology of receptor–ion channels involved in pain transmission). Chapter 8 examines phenotype regulation of dorsal root ganglion neurones after nerve injury. This is an excellent and thought provoking review of the literature with many of the 153 references from the authors themselves. Chapter 9 was also an interesting read which followed on well.

Chapters 13 and 14 covering Na^+ channels and opioid receptors were particularly interesting to me as this is in my own area of interest. In addition, I would also strongly recommend careful reading of chapter 17 on antisense technology. The volume is rounded off nicely with a chapter on gene transfer in pain control, opening up a whole new avenue for future pain therapies.

If I were to note any omissions these would include a chapter on orphan-opioid receptor (ORL1)-nociceptin and pain, and voltage-gated Ca^{2+} channels and pain. Omission of ORL1-nociceptin is likely a result of timing as the meeting was held in 1996, just 1 yr after the description of nociceptin. In addition, this book probably went to press before the IUPHAR reclassified opioid receptors as $OP1(\delta)$, $OP2(\kappa)$ and $OP3(\mu)$.[1]

In all, this is an excellent read. I strongly recommend this book to all involved in opioid–pain research. This volume will also be of use to those candidates preparing for the FRCA examinations or equivalent.

D. Lambert

1. Dhawan BN, Raghubir CR, Reisine T, Bradley PB, Portoghese PS, Hamon M International union of pharmacology. XII. Classification of opioid receptors. *Pharmacology Reviews* 1997; **48**: 567–592.

Fundamentals of Anaesthesia and Acute Medicine. Paediatric Intensive Care. A. DUNCAN (editor). Published by BMJ Publishing Group, London. Pp. 276; indexed; illustrated. Price £30 00.

This book forms part of a series entitled *Fundamentals of Anaesthesia and Acute Medicine* which aims to provide authoritative reviews of topics in selected areas of clinical practice. The series is aimed at established practitioners and trainees preparing for diplomas in anaesthesia and intensive care. The present volume will be of particular interest to consultants and trainees who are involved in the provision of intensive care for critically ill children.

It is edited by Alan Duncan from Perth, Australia, who has succeeded in assembling an eminently readable volume which covers current practice and recent advances in several key areas of paediatric intensive care medicine. There are nine chapters written by internationally renowned experts in paediatric intensive care, and most of the topics have a major bearing on morbidity and mortality.

The first chapter comprises a characteristically robust exposition by Dr Frank Shann summarizing recent work investigating the effects of organization of paediatric intensive care services on patient outcome; there is also a useful description and critique of the currently available risk adjustment methods used in paediatric intensive care. This is followed by a chapter on acute respiratory emergencies which contains a wealth of information, including several useful tables, charts and algorithms. Desmond Bohn from Toronto contributes a chapter on new ventilation strategies which is characteristically lucid, thorough and well informed. The pathophysiology of respiratory failure is described, together with a comprehensive survey of the work on ventilator-induced lung injury. There are clear descriptions of all currently available methods used for supporting children with acute respiratory failure, including innovative techniques such as high frequency ventilation, nitric oxide, liquid ventilation and extracorporeal membrane oxygenation. Dr Bohn subjects the research on these topics to rigorous but constructive critical analysis. It is likely that greater facility in the use of these newer therapies should help to optimize management and lead to a reduction in the requirement for ECMO among infants and children.

A separate chapter devoted to nitric oxide summarizes the research which has been undertaken into the use of this agent in children. There is also useful information on administration, monitoring and toxicity of nitric oxide.

The increasing problem of children who require long-term ventilation is addressed in a chapter which covers ethics, practicalities, economics and the indications for home ventilation. Although details of some useful Internet sites are included at the end of this chapter, I would have liked to have seen greater use of charts, tables and checklists which would be of particular help for those who have to make arrangement for the management of children requiring long-term ventilation in the community.

A chapter by Duncan Macrae provides invaluable information on the presentation, diagnosis and early management of congenital heart disease, together with strategies for the management of low cardiac output and pulmonary hypertension. There are also useful chapters on "Management of paediatric trauma" and "Acute brain insults in infants and children". Finally, there is an authoritative chapter by Warrick Butt which brings together the latest thinking on the management of septic shock in children, with particular reference to the ever present problem of meningococcal disease.

The subjects included in this book cover a very wide range, ideally, I would have liked to have seen a section covering the provision of analgesia and sedation in the paediatric intensive care unit. Each chapter includes numerous recent references, however there are minor inaccuracies in some of the references appended to the chapters on nitric oxide and septic shock.

I detected one error in the text on page 202 where it states: "Inhibition of NO synthesis increases pulmonary blood flow and increased pulmonary vascular resistance in the perinatal period". The quality of the printing, tables, graphs and charts is generally very high, although I was disappointed that my review copy showed evidence of poor binding, a number of pages becoming partially detached. This possible reflects the fact that I have found the book to be an invaluable reference source and repository of information.

This is an excellent book and the editor has succeeded in assembling an attractive and stimulating text which, in 276 pages, provides a wealth of up-to-date information on the management of critically ill children with a wide variety of conditions. It can be recommended to those looking for a modern and authoritative account of the more significant recent developments in paediatric critical care medicine.

N. R. Bennett

Who Cares? The Great British Health Debate. O. MORGAN. Published by Radcliffe Medical Press, Abingdon. Pp. 231; indexed.

It will have escaped the attention of few doctors, certainly none who have read or seen recent media contributions by the editor of the *Lancet*, Dr Richard Horton, that the profession is under attack. In this 50th anniversary year of the NHS, the "doctor knows best" school of patient care does not carry the confidence of the public, and patients are not necessarily as grateful for any bestowed crumb of charity as they were in 1948. The Royal Colleges are being portrayed as irrelevant gentlemen's clubs and the BMA as seeking to perpetuate the power and self-interest of the medical profession. And the hounds are baying for blood in the form of accountability, outcomes and clinical governance. Or so it seems, and just because we are paranoid doesn't mean they are not out to get us!

Perhaps it was in this frame of mind that I picked up Oliver Morgan's contribution to the *Great British Health Debate*. My initial impressions were a mixture of great admiration for an extremely well researched, clear volume on the British health system and yet a concern for the selective application of "facts" by an experienced journalist making his case Within its well referenced 231 pages you will find clear descriptions of the nuances of maximum part-time consultant contracts, notional half-days and job plans. Those who are old enough will recognize, perhaps even nostalgically, the consensus of cogwheel structures, the Griffiths introduction of management reforms and, finally, the internal market.

Mr Morgan recognizes the central role of doctors in the future of a viable NHS and wants them to manage resources effectively in the light of accurate information. The dilemma of shifting resources for the good of a population without damaging the individual doctor–patient relationship is tackled if not resolved, and suggestions of citizens' juries and focus groups are helpful. What is not sufficiently developed is how involving the general public can be used to put some brakes on expectation and demand, to tighten the tap on the pressure of the worried well. The media oscillate between "top doctors find elixir of life" and "hospital misses cancers shock", and some steadying influence is urgently needed.

Where the medical profession will again feel under attack is Mr Morgan's recurring theme that doctors are resisting the development of proper audit with measurable outcomes, assessments of effectiveness and proper accountability. In this "post-Bristol" epoch, it is our duty to prove Mr Morgan's concerns unfounded by taking on the challenge of clinical governance, to drive its agenda and to show that self-regulation is not synonymous with cosy self-interest.

You will find many stimulating opportunities and threats in Oliver Morgan's vision for the next 50 yr.

I. Gilmore

Interactive Anesthesia Library on CD-ROM version 2.0. P. G BARASH. Published by Lippincott-Raven, Philadelphia. Indexed; illustrated. Price US$395.00.

This remarkable CD-ROM contains the full text and figures of seven major American textbooks· *Textbook of Internal Medicine*; *Clinical Anesthesia*; *Handbook of Clinical Anesthesia*; *Review of Clinical Anesthesia*; *Pharmacology and Physiology in Anesthetic Practice*; *Neural Blockade*; and *Anesthesiology: Problem-Orientated Patient Management*. All except the latter two are current editions of these books. This amounts to nearly 8000 pages of text and 3000 images, in addition to several video clips of key procedures and diagnostic situations. In addition, the Anesoft Anesthesia desktop simulator is included in an impressive package. The CD is both Windows and Mac compatible and the recommended minimum system requirements are a Pentium or PowerMac processor with 8 MB RAM, with video and sound cards, double-speed CD-ROM drive and 3 MB of free hard disk space. Installation of the software is very straightforward and the accompanying instructions are easy to follow.

In such a large source of reference material the search functions have to be intuitive and effective. Fortunately, navigation is easy and rapid searches are possible using a string of key words. Advanced searching techniques using Boolean logic, wildcard searches and proximity searches can also be used. Either the whole database, or individual titles within it, can be searched, and this improves flexibility. The on-line help is very good with many useful hypertext links which give clear explanations. There is also a quiz facility for testing knowledge gained from specific chapters that might be of interest to readers preparing for examinations

For any multimedia package to be attractive, and to justify its significant cost, it has to be more than a book on CD. High quality and relevant audiovisual clips are a must, but this package has only 13 titles listed in the video highlights section and more would be welcome. Topics covered include fibreoptic laryngoscopy, retrograde intubation, cricothyroidotomy, a variety of peripheral nerve blocks and some interesting transoesophageal echocardiograms. The video image quality is high, even on a notebook PC, but the British user may find the American commentary distracting.

The Anesoft anaesthesia simulator consists of four clinical scenarios that can be customized to include a range of critical incidents if required. Inevitably, the terminology used is American, but that does not really matter. The simulator desktop includes a photograph of the patient and a monitor screen showing ECG, capnography and any other traces selected by the user. There are menus for changing the monitoring, fluids, airway, ventilation, drugs administered and surgical interventions, although control over the latter may be the least realistic option! Using the simulator is fun, but not particularly educational, although each case has specific learning objectives that can be viewed at any time. Like most desktop simulators it lacks realism and is cumbersome to use. It also lacks any sound so the user is denied the usual audio clues which are available in the clinical setting.

Printing and exporting text and images from the CD-ROM is simple. Images pasted onto PowerPoint slides projected well and this could be useful when preparing lectures or tutorials, but the copyright position on this is not clear.

It is possible to apply personal bookmarks and highlight favourite areas of text which is a useful way to return to areas of interest. The user can also annotate text by adding their own "sticky notes" in the same way as one might jot in the margin of a book. The notes are searchable and so can be found quickly again.

This CD-ROM contains a staggering amount of information and illustrates what the strengths of this format are, namely portability and searchability. The cost may seem expensive but the total retail cost of the books included would be more than £500. The product is seriously worth considering if the departmental library fund has anything left in it

M. R. Checketts
J. A. W. Wildsmith

Getting Ahead in Medicine: A Guide to Personal Skills for Doctors. C. JOHNSON, F. FORREST AND C. HALL. Published by Bios Scientific Publishers, Oxford. Pp. 178; indexed; illustrated. Price £17.95.

This paperback presents the type of information which is gained only after the passage of many years but which we all wish we knew when we started out on our careers. As the authors suggest, it represents the distillation of many years spent advising junior colleagues at all levels on what is expected of them and how to improve their chances of being able to select the type of post which they would want, rather than that which would be offered to them. The introduction advises dipping into sections which are relevant to the individual rather than starting at page one and progressing through all chapters. I tried this and was surprised at the overall value of this approach. However, a reviewer's duty is to assess the complete book rather than to surf what appear to be only the more interesting sections.

The title of this book suggests that it should perhaps contain techniques or tips to succeed in the rat race of hospital politics, but nothing could be further from the truth. The preface explains the background to the book and it perhaps should have been entitled: *A really practical guide for trainees in medicine*. There are very few books which precisely achieve its aims and in such a slim volume. The authors set out to produce a guide to the intricacies of starting as a trainee in hospital, the expectations of trainers and the problems of understanding the organization and society in which the trainees now find themselves. The book is divided into the types of information which would be required at different stages of the trainee's career. There are four different skill levels, ranging from advice which is appropriate for students and pre-registration house officer, up to that which would be of interest to experienced trainees or consultants.

The first sections describe how to obtain a post, the factors which influence short listing and the final selection of candidates, and how to improve one's chance of success. Time management is one area in which possibly most doctors are deficient and many consultants could benefit from reading this section. The new structured training system is explained, as is the way that trainees should approach their learning, not only for examinations but also to ensure long-term education throughout their professional careers. The value of undertaking research and the approach necessary to obtain worthwhile results are fully explained in addition to how to write up the final results for publication. The final chapter leads the reader into the area of medical ethics and uses several court cases to explain the basis of the changing relationship between medicine and society.

Overall the book is clearly written and succinct. It contains sensible advice and it is apparent that the book has been written based on the questions which trainees have asked the authors over past years. The section describing the structure of a computer is perhaps too detailed, but the steps by which the trainee should use a program such as PowerPoint to produce their own overhead transparencies or 35-mm slides should guarantee success for the beginner.

Every trainee should know about this book and should have access to it. It does not replace the mentor but it probably has a broader base than most mentors have of information which will be relevant to the trainee during their passage through the training system.

G. N. C. Kenny

Clinical Anesthesia, 3rd Edn. P. G. BARASH, B. F. CULLEN AND R. K. STOELTING (editors). Published by Lippincott-Raven, Philadelphia Pp. 1483; indexed; illustrated. Price US$145.00.

There are now many large textbooks of anaesthesia on the market and it is inevitable that competition will ensure that some do not survive. The size of the North American market dictates that success may be more assured if contributors are drawn from both North America and Europe and that formula may be seen in well-known texts which appear to have been edited Mid-Atlantic.

Clinical Anesthesia is a predominantly American production with 100 contributors, of whom 95 are based in the US, three in Canada, two in Ireland, one in Germany and one in Belgium. It is a very cost-effective production containing more than 1400 pages and is inexpensively priced. Clearly, the cost of production has been constrained by the use of a small font, light-weight paper, but although well-illustrated, many of the figures and especially the photographs are of poor quality. In particular, I studied the chapter on "Peripheral nerve blockade" and believe that it would be difficult to use any of the diagrams contained in this chapter as aids in the practical performance of regional blocks.

Most large multi-author texts suffer from the disadvantage of variability in quality, extent of detail and referencing. However, this particular text achieves as good a level of balance as possible in these respects. There is an adequate synopsis of basic physiology and pharmacology where necessary, for example a separate chapter on cardiovascular anatomy and physiology precedes the chapter on anaesthesia for cardiac surgery, and there are good accounts of renal physiology in the section on urological surgery, and endocrine physiology in the chapter on anaesthesia and the endocrine system, etc. It was pleasing to see some lack of parochialism in referencing.

This is not a detailed reference book for those who wish to research a topic in detail. However, it is one of the better large textbooks of anaesthesia and is to be recommended to residents, including those studying for both the Primary and Final FRCA examination or equivalent. For those who are contemplating purchasing a textbook for this purpose, the cost of *Clinical Anesthesia* makes it a serious candidate for consideration and one which I can thoroughly recommend.

G. Smith

A Short History of the Section of Anaesthetics of the Royal Society of Medicine and the Society of Anaesthetists. T. M. YOUNG. Published by the Royal Society of Medicine, London. Pp. 222. Price £19.50 (£17 at the Section of Anaesthetics Meeting).

Those anaesthetists who are regular attenders at the Section of Anaesthesia meetings will find this small, privately printed, volume a mine of fascinating information. Described by its author as "essentially a reference work rather than an easy read", it initially gives an intriguing insight into the intellectual state of Medical London in the years around the turn of the last century, which resulted in the formation of the Royal Society of Medicine in 1907. It is interesting to note that at a time when womens' rights were minimal, the Society of Anaesthetists, who admitted women to full membership, needed assurances that women would be admitted to full Fellowship of the RSM, and not be confined merely to membership of the Section, before agreeing to be dissolved in 1908 to become the Section of Anaesthetics of the RSM. The role of women in the affairs of the Section over the years is noted by the author. The significance of the Sections within the RSM was that this type of organizational structure accorded each speciality group (or Section) full recognition as a speciality, and as such each became equal citizens within the Societies House (An attitude of mind that did not appear to spread too far from 1, Wimpole Street until 1948 and the arrival of the NHS.)

Brief sections then follow on various aspects of the Section's activities over the years, ranging from attendances at meetings, topics covered in meetings and the use of audio-visual aides, to name but a few. Browsing through these sections, readers might be forgiven for thinking that there is little new in life—only the names change! There is a useful chart describing the pedigree of the Section of Anaesthetics, and in the section "Foundation of sister societies" the development of the Association of Anaesthetists of Great Britain and Ireland and the Faculty of Anaesthetists is discussed briefly. The main body of the text is short (approximately 22 pages), followed by a series of appendices listing details of the activities, and office holders, of the Society of Anaesthetists and the Section of Anaesthetics (192 pages).

This book will be a useful addition to the historical section of any departmental library, but those who have been actively involved with the Section will not regret purchasing their own copies.

I. M. Corall

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EDITORIAL

Opioids and the immune system

There has been growing interest in the significance of neuropeptides in the immune system which has resulted in the recent publication of an editorial[1] and review[2] which are deserving of interest within the anaesthetic community. There is now a considerable body of literature which demonstrates a modulatory function of the immune system by opioids. This modulation takes the form of an alteration in the biochemical and proliferative properties of the various cellular components of the immune system. As many of the mechanisms and molecules are almost identical within vertebrates and invertebrates, it would seem that opioid peptide immunoregulatory mechanisms first evolved in primitive organisms. Because they have been conserved, it would suggest that this remains a highly significant mechanism in humans.

Opioid precursors have been isolated and sequenced from a variety of invertebrate species (most work has been performed in the leech and marine mussel) and these have a very close sequence homology with the mammalian counterpart molecules. For instance, there is a 119 amino acid prodynorphin-like molecule which has an identical number of [Leu]enkephalin sequences to that of mammals. The leech has been shown to produce a mammalian-like pro-opiomelanocortin (POMC) molecule, and six of its peptides, including adrenocorticotropin (ACTH), a-melanocyte-stimulating hormone (a-MSH) and [Met]enkephalin. The proenkephalins from the leech and marine mussel possess [Met] and [Leu]enkephalins with relevant cleavage sites. In addition, opioid binding experiments have shown that delta 1 and delta 2 opioid receptor subtypes (in common with those in humans) are present in leech ganglia and immunocytes, and mussel immunocytes.[3]

Vertebrates and invertebrates have been shown to possess a peptide which is a proenkephalin and has a strong antibacterial action.[4] This peptide is called enkelytin (proenkephalin-A) and there is a strong sequence homology between invertebrate and mammalian enkelytin.[5] The presence of this strongly antibacterial enkelytin further strengthens the association between opioid peptides and the immune system. It has been suggested that immune or neural signalling leads to enhanced proenkephalin proteolytic cleaving thereby causing the release of both opioid peptides and enkelytin simultaneously. This scenario would allow a two-pronged attack. Opioid peptides would modulate neutrophil chemotaxis, phagocytic activity and the secretion of cytokines, while the simultaneously liberated enkelytin would exert an antibacterial action.

Because of the involvement of the peripheral and central nervous systems with immune function it now becomes feasible to consider the link between pain and the immune system. A unified response to a painful stimulus which would include a sensing mechanism providing an initial avoidance response, together with a later local analgesic response in the tissues from endogenous opioids,[6] and which is associated with the release of potent antibacterial peptides,[5] is an ideal scenario. A similar pattern may exist in humans.[7]

Corticotropin releasing hormone (CRH) is an important hormone released under stress conditions from both the hypothalamus and cells of the immune system. Injection of CRH has been shown to produce analgesia when injected into sites of local inflammation, an effect which is blocked by co-injection of antiserum to β-endorphin.[8] This again suggests a possible mechanism whereby local activation of the endogenous opioid system from immunocompetent cells provides both an analgesic action and anti-inflammatory effect.

Further evidence for the role of immune cells in pain control pathways comes from work in rats following injection of antigen to induce inflammation in a paw. Concentrations of β-endorphin were found to increase in peripheral tissues while concentrations in the lymph nodes which were previously high, decreased.[9] It is suggested that T lymphocytes may be acting as vectors for β-endorphin to inflamed tissues. The significance of this hypothesis is that it would allow the potential for highly specific opioid control of peripheral analgesia by targeted delivery of β-endorphin directly to sites of inflammation. This would maximize the potential analgesic and anti-inflammatory effects of endogenous opioids acting at peripheral receptors and also by inhibiting the release of the inflammatory peptide substance P from primary afferent neurones.[10]

It is also possible that opioids released from cells of the immune system may modulate release of cytokines from the same and other cells of the immune system.[11] Beta-endorphin, [Met]enkephalin and [Leu]enkephalin have been shown to inhibit the secretion of the pro-inflammatory cytokine interleukin-6 (IL-6) from mouse spleen.[12] Also, IL-6 production from activated peripheral blood mononuclear cells is decreased by opioid peptides.[13] On the other hand, cytokines have been shown to regulate opioid formation in neural tissue culture experiments. Interleukin-1β increases μ opioid receptor mRNA in cultured rat astrocytes and decreases proenkephalin mRNA in hippocampal cultures.[14 15]

Proenkephalin mRNA and proenkephalin derived peptides have been reported in human lymphocytes, monocytes and macrophages. [Met]enkephalin is released by human peripheral blood lymphocytes which have been activated by phytohaemagglutinin. Experiments using a blocking antibody to enkephalin demonstrated decreased DNA synthesis in stimulated human lymphocytes.[16] However, others have shown that delta opioid receptor agonists dose dependently inhibit the proliferation of cultured CD4+ and CD8+ T-cells from mice.[18] A study using specific μ, δ and κ opioid receptor agonists have shown that they result in significantly decreased immunoglobulin production by activated human B lymphocytes.[13] Perhaps these different results are caused by the effect of different cell types, different species studied or because of the differing effects of the various receptor subtypes.

In addition, there is much interest in the ability of chronic opioid use to modify the immune system. Much of this work stems from the observation that parenteral drug abuse is a significant risk factor for contracting human immunodeficiency virus type I (HIV-1). Chronic morphine treatment is a mechanism used in laboratory experiments to render mice immunocompromised.[18] Morphine significantly decreases in a dose dependent manner the proliferation of stimulated human lymphocytes in addition to reducing the production of IFN-α and IFN-β, an effect reversed by naloxone.[19] Gamma interferon-stimulated natural killer cell cytotoxicity is significantly suppressed after short-term exposure to morphine in humans.[20]

There is now a substantial body of evidence which demonstrates that opioids and endogenous opioid peptides modulate immune function. Moreover, inflammatory mediators have been shown to modify the release of opioid peptides from immune system cells and also from cells of the peripheral and central nervous system. The potential effects of exogenously administered opioids on the immune system cannot be ignored. Variations in postoperative infection rate have not to date been attributed exclusively to the use of perioperative opioids as there are many other compounding factors. However, it would seem most likely that opioid use in both the surgical patient and the critically ill would have a profound immunomodulatory effect and we should be cognizant of this effect when we chose our anaesthetic, analgesic or sedative technique.

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References

1. Jessop DS. β-endorphin in the immune system—mediator of pain and stress? *Lancet* 1998; **351**: 1828–1829.
2. Stefano GB, Salzet B, Fricchione GL. Enkelytin and opioid peptide association in invertebrates and vertebrates: immune activation and pain. *Immunology Today* 1998; **19**: 265–268.
3. Salzet M, Stefano GB. Invertebrate proenkephalin: delta opioid binding sites in leech ganglia and immunocytes. *Brain Research* 1997; **768**: 224–232.
4. Strub JM, Goumon Y, Lugardon K, Capon C, Lopez M, Moniatte M, Van Dorsselaer A, Aunis D, Metz-Boutigue MH. Antibacterial activity of glycosylated and phosphorylated chromogranin A-derived peptide 173–194 from bovine adrenal medullary chromaffin granules. *Journal of Biological Chemistry* 1996; **271**: 28533–28540.
5. Goumon Y, Strub JM, Moniatte M, Nullans G, Poteur L, Hubert P, Van Dorsselaer A, Aunis D, Metz-Boutigue MH. The C-terminal biphosphorylated proenkephalin-A-(209–237)-peptide from adrenal medullary chromaffin granules possesses antibacterial activity. *European Journal of Biochemistry* 1996; **235**: 516–525.
6. Zadina JE, Hackler L, Ge LJ, Kastin AJ. A potent and selective endogenous agonist for the mu-opiate receptor. *Nature (London)* 1997; **386**: 499–501.
7. Przewlocki R, Hassan AHS, Lason W, Epplen C, Herz A, Stein C. Gene expression and localisation of opioid peptides in immune cells of inflamed tissue: functional role in antinociception. *Neuroscience* 1992; **48**: 491–500.
8. Schafer M, Mousa SA, Stein C. Corticotropin-releasing factor in antinociception and inflammation. *European Journal of Pharmacology* 1997; **323**: 1–10.
9. Cabot PJ, Carter L, Gaiddon C, Zhang Q, Schafer M, Loeffler JP, Stein C. Immune cell-derived β-endorphin. Production, release, and control of inflammatory pain in rats. *Journal of Clinical Investigation* 1997; **100**: 142–148.
10. Jessop DS. Neuropeptides: modulators of the immune system. *Current Opinions in Endocrinology and Diabetes* 1998; **5**: 52–58
11. Carr DJJ, Rogers TJ, Weber RJ. The relevance of opioids and opioid receptors on immunocompetence and immune homeostasis. *Proceedings of the Society for Experimental Biology and Medicine* 1996; **213**: 248–257.
12. Straub RH, Herrmann M, Berkmiller G, Frauenholz T, Lang B, Scholmerich J, Falk W. Neuronal regulation of interleukin 6 secretion in murine spleen: adrenergic and opioidergic control. *Journal of Neurochemistry* 1997; **68**: 1633–1639.
13. Morgan EL. Regulation of human B lymphocyte activation by opioid peptide hormones. Inhibition of IgG production by opioid receptor class (mu-, kappa-, and delta-) selective agonists. *Journal of Neuroimmunology* 1996; **65**: 21–30.
14. Ruzicka BB, Akil H. The interleukin-1 beta-mediated regulation of proenkephalin and opioid receptor messenger RNA in primary astrocyte-enriched cultures. *Neuroscience* 1997; **79**: 517–524.
15. Ruzicka BB, Thompson RC, Watson SJ, Akil H. Interleukin-1 beta-mediated regulation of mu-opioid receptor mRNA in primary astrocyte-enriched cultures. *Journal of Neurochemistry* 1996; **66**: 425–428.
16. Padros MR, Saravia F, Vindrola O. Antibodies against the amino-terminal portion of pro-enkephalin inhibit DNA synthesis in human peripheral mononuclear cells. *Journal of Neuroimmunology* 1995; **61**: 79–83
17. Shahabi NA, Sharp BM. Delta opioid agonists inhibit proliferation of highly purified murine CD4+ and CD8+ T-cells *Advances in Experimental Medicine and Biology* 1995; **373**: 29–36.
18. Di Francesco P, Gaziano R, Casalinuovo IA, Palamara AT, Favalli C, Garaci E. Antifungal and immunoadjuvant properties of fluconazole in mice immunosuppressed with morphine. *Chemotherapy* 1997; **43**: 198–203.
19. Nair MP, Schwartz SA, Polasani R, Hou J, Sweet A, Chadha KC. Immunoregulatory effects of morphine on human lymphocytes. *Clinical and Diagnostic Laboratory Immunology* 1997; **4**: 127–132.
20. Yeager MP, Colacchio TA, Yu CT, Hildebrandt L, Howell AL, Weiss J, Guyre PM. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. *Anesthesiology* 1995; **83**: 500–508.

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CLINICAL INVESTIGATIONS

Concentration and second-gas effects in the water analogue

W. W. Mapleson and B. Korman

Summary

The water analogue provides a visual model of the process of anaesthetic exchange. In the standard version, a single pipe connects the mouth container to the lung container and the conductance of this mouth–lung pipe is proportional to alveolar ventilation. This implies that inspired and expired ventilations are equal. In fact, with high inspired concentrations of nitrous oxide, early rapid uptake of gas by solution leads to a substantial difference between inspired and expired ventilation which in turn leads to concentration and second-gas effects. It is shown that by representing inspired and expired ventilations separately, and keeping one of them constant while varying the other to compensate for rapid uptake, concentration and second-gas effects are reproduced in the water analogue. Other means of reproducing the effects are reported but we believe that the first method is the most realistic and the most appropriate for teaching. (*Br. J. Anaesth.* 1998; **81**: 837–843)

Keywords: anaesthetics volatile; anaesthetic gases, nitrous oxide; pharmacokinetics, uptake; pharmacokinetics, nitrous oxide; model, lung; model, water analogue

It is obvious that, in general, the greater the inspired concentration of an inhaled anaesthetic the more rapid the induction. However, even the approach of the alveolar concentration towards the inspired concentration is more rapid at high inspired concentrations than at low. This has been termed the "concentration effect".[1–3] Also, when an anaesthetic agent is used at a low concentration (e.g. isoflurane), its alveolar concentration increases more rapidly when the carrier gas contains a high concentration of an anaesthetic which is itself subject to the concentration effect. This has been termed the "second-gas effect".[4]

These effects are well known but poorly understood. Most explanations are based on Stoelting and Eger's rectangle diagram.[5] A previous review[6] pointed out some deficiencies in these explanations and showed how these could be overcome by an improved rectangle diagram. This article explores how these effects can be explained in terms of the water analogue.

Methods

THE BASIC WATER ANALOGUE AND ITS DEFICIENCIES

The basic form of the water analogue of the uptake and distribution of inhaled anaesthetics is illustrated in figure 1 for nitrous oxide. Full accounts of this basic form are available[7–9] but briefly, the nature of the analogy is as follows. The water represents the anaesthetic itself—ml of water corresponding to, say, mmol of anaesthetic. The constant head of water in the overflowing "mouth" container represents a constant inspired concentration—mm head of water corresponding to, say, percent concentration. The water level in the lung container represents the concentration in that compartment and the level in each tissue container represents the gas-phase concentration with which that tissue is or would be in equilibrium. Alternatively, the water levels can all be interpreted as partial pressures, so that each level indicates partial

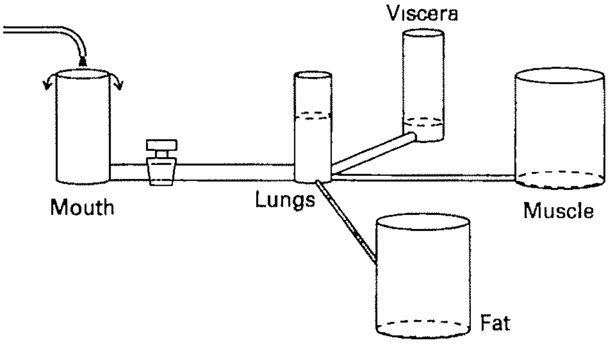

Figure 1 The basic form of the water analogue of the uptake and distribution of an inhaled anaesthetic, scaled to represent a 70-kg patient[19] being anaesthetized with nitrous oxide; alveolar ventilation and cardiac output are 4 litre min^{-1} and 5 litre min^{-1}, respectively; FRC=2 litre. The width of each pipe corresponds to the transporting ability of the alveolar ventilation (mouth–lung pipe) or blood flow (lung–tissue pipes) for the agent[11 20]; the cross-sectional area of each container is proportional to the specific storage capacity of the tissue group for the particular agent (amount stored per unit partial pressure). Therefore, the width of each container is proportional to the square root of its specific storage capacity. Accordingly, to give the right visual impression, the widths of the pipes (which are all the same length) have been made proportional to the square root of their transporting abilities. (For a working water analogue, the fourth root would be required.) The constant head of water in the overflowing mouth container represents a constant inspired concentration and hence a constant inspired partial pressure. The water levels in the lung and tissue containers represent the concentrations or partial pressures in those compartments as fractions of that inspired concentration or partial pressure (For the tissues, concentration must be taken to mean the gas-phase concentration with which the tissue is or would be in equilibrium.) Water levels were calculated by a computer model[9] adapted to match this basic form of the water analogue, that is without allowing for the concentration effect, to illustrate conditions after 1 min administration of nitrous oxide

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pressure as a fraction of the inspired partial pressure. (All the containers have been made the same height so that those fractions and their differences are readily apparent.) The cross-sectional areas of the containers represent the specific storage capacities of the compartments for the anaesthetic (i.e. the amount stored *per unit partial pressure*, for example mmol of anaesthetic per atmosphere partial pressure in the compartment). The total amount of anaesthetic present in the compartment at any time is equal to the specific storage capacity multiplied by the partial pressure there at that time. The pipe between the mouth and lung containers represents alveolar ventilation; the pipes between the lung container and the tissue containers represent blood flow to each group of tissues. (More precisely, these pipes, which are all the same length, represent the transporting abilities of ventilation and blood flows for the particular anaesthetic, for example mmol per min of anaesthetic per atmosphere partial pressure difference from mouth to lungs or from lungs to tissues.) Movement of water between containers occurs in response to pressure differences which exist until equilibrium is reached.

When the tap on the mouth–lung pipe is first opened, water flows from the mouth container, through the pipe to the lung container where the water level begins to rise; correspondingly, when the vaporizer is turned on, or when nitrous oxide is added to the inspired mixture, anaesthetic is conducted by alveolar ventilation to the lungs where the concentration of anaesthetic begins to rise. As the water level in the lung container rises, water is conducted by the connecting pipes to all tissue containers where the water levels also begin to rise; correspondingly, as the concentration of anaesthetic in the alveoli rises, anaesthetic dissolves in blood flowing through the lungs and is transported to all tissues where concentrations begin to rise. Eventually, the water levels come into equilibrium with that in the mouth container; that is, neglecting metabolism and any loss through skin or operation wound, all tissue concentrations come into equilibrium with the inspired concentration (if that is held constant for long enough) and all partial pressures become the same as the inspired partial pressure. Anaesthesia is induced when a certain threshold partial pressure is exceeded in the brain, represented here as a component of the viscera compartment.

In principle, the water analogue could be used for quantitative computation. However, its main justification is the facilitation of "thought experiments", whereby altering features of the analogue to match assumed changes in administration of an anaesthetic, or changes in the patient, can be seen to produce changes in the rates of uptake and in concentrations which correspond qualitatively to what happens in reality. Used in this way, the water analogue can explain a large number of clinically observed phenomena.[8 9] However, it has a deficiency.

According to the theory of the basic water analogue,[7] an increase from 1% to 70% inspired concentration can be achieved without making any changes to the containers and pipes of the analogue: it is sufficient to assume that the height of the mouth container now represents 70 times the concentration that it did before, provided that each ml per min flow of water is also assumed to represent 70 times the rate of uptake of nitrous oxide as previously. These assumptions obviously have no effect on the speed of equilibration of water in the analogue. Therefore, the basic water analogue suggests that the time to reach equilibrium, or any given degree of equilibrium, is independent of the inspired concentration; this is contrary to the concentration effect.

THE REASON FOR THE DEFICIENCY IN THE BASIC WATER ANALOGUE

The reason for this deficiency is as follows. There are two aspects to the uptake of anaesthetic by solution in blood flowing through the lungs: one aspect is removal of molecules of anaesthetic from the lungs, and this is faithfully represented by the water analogue—ml per min of water flowing out of the lung container corresponding to, for example mmol per min of anaesthetic dissolving in blood flow. The other aspect is removal of gas volume from the lungs. When the inspired concentration is only a few percent, the volume removed by solution is only a few ml per min but, with 70% nitrous oxide, it can increase rapidly to a peak rate of approximately 1 litre min^{-1}.[10–12] It is this rapid removal of gas by solution that results in concentration and second-gas effects.

One possible consequence of the rapid volume uptake is a decrease in functional residual capacity (FRC). However, any such decrease amounts to only a few hundred millilitres.[6 13] If we neglect this small amount, then instead of the inspired and expired ventilations being approximately equal as in normal respiration, the expired ventilation is substantially less than the inspired ventilation, either by the expired ventilation decreasing or by the inspired ventilation increasing, or a combination of the two.

In the water analogue, the flow of water through the mouth–lung pipe is equal to $(F_I - F_A) \times \dot{V}_A$, where F_I is the head of water in the mouth container (the pressure at its base), F_A is the head of water in the lung container, and V_A is the conductance of the connecting pipe. (Conductance is flow per unit pressure difference—the reciprocal of resistance.) This therefore represents the rate of uptake of anaesthetic from mouth to lungs where F_I and F_A are now the inspired and alveolar concentrations and $\dot{V}_A$ is alveolar ventilation.

Note that the net rate of uptake $(F_I - F_A) \times \dot{V}_A$ is the difference: flow of anaesthetic into the lungs in inspiration, $F_I \times \dot{V}_A$, minus flow out in expiration, $F_A \times \dot{V}_A$. (Deadspace ventilation can be ignored because it goes into and out of the lungs without any change in its anaesthetic content.)

Similarly, the flow of water through, for instance, the lung–muscle pipe is equal to $(F_a - F_m) \times \lambda \times \dot{Q}_m$, where F_a and F_m are the heads of water in the lung and muscle containers and $\lambda \times \dot{Q}_m$ is the conductance of the connecting pipe. This therefore represents the rate of uptake of anaesthetic from lung to muscle where F_a is the gas-phase concentration with which arterial blood is in equilibrium (assumed to be the alveolar concentration), F_m is the concentration with which the venous blood leaving the muscle would be in equilibrium (assumed to be the same as that for the muscle itself), λ is the blood/gas partition coefficient, and $\dot{Q}_m$ is the flow of blood through the muscle tissues. Here the net rate of uptake $(F_a - F_m) \times \lambda \times \dot{Q}_m$ is the difference between the flow of anaesthetic from lung to muscle in arterial blood, $F_a \times \lambda \times \dot{Q}_m$, minus the return of anaesthetic from muscle to lung in venous blood, $F_m \times \lambda \times \dot{Q}_m$.

This method of representing uptake, into the lungs and then into the tissues, is adequate for blood because the flow of blood to a tissue is essentially equal to the return flow from the tissue. On the other hand, for alveolar ventilation, the approach is inadequate because the inspired alveolar ventilation is not equal to the expired, except when the volume rate of uptake from lungs to tissues is negligible.

OVERCOMING THE DEFICIENCY

It is possible to elaborate the basic water analogue to show the inspired and expired alveolar ventilations separately (fig. 2). The mouth container and attached pipe are now separated from the lung container and raised above it. The height of water in the mouth container still represents the inspired concentration, F_I, but the pipe leading from it now represents only the inspired alveolar ventilation, $\dot{V}_{AI}$. There is no back pressure at the right-hand end of the pipe so, when the tap is opened, the flow through it is $F_I \times \dot{V}_{AI}$ and this enters the lung container. This flow of water therefore represents the flow of anaesthetic into the lungs in the inspired ventilation. The lung container still has a ventilation pipe connected to it, but this now represents only the expired alveolar ventilation, $\dot{V}_{AE}$. Its end is open, so water flows out at a rate of $F_A \times \dot{V}_{AE}$, thereby corresponding to the flow of anaesthetic out of the lungs in the expired ventilation.

Figure 2 depicts the condition before the anaesthetic has started: the on–off tap is closed and both ventilation pipes are the same width as the single pipe in figure 1. When an inhalation anaesthetic is used at low concentrations, the rate of uptake by solution is always small, so there is a negligible change in the ventilation pipes: the analogue in figure 2 behaves in the same way as that in figure 1 which is therefore adequate for low inspired concentrations. However, when the anaesthetic is nitrous oxide at a high concentration, the rate of uptake soon becomes large and a substantial difference develops between the widths of the two ventilation pipes. It is from this difference that the concentration and second-gas effects arise (see below).

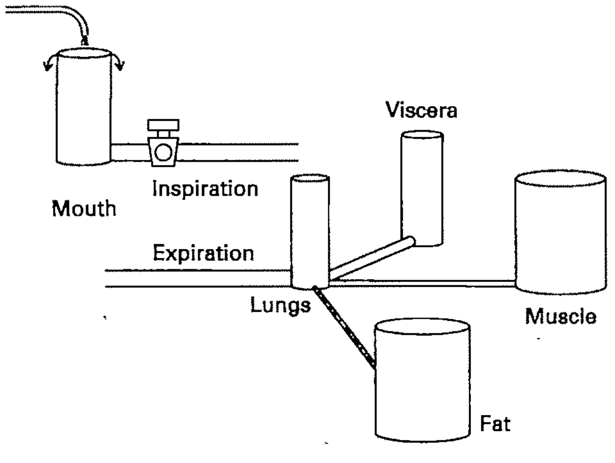

Figure 2 The basic water analogue, pictured before the anaesthetic has started and elaborated to represent inspired and expired alveolar ventilation separately. The inspired and expired ventilation pipes both have the same dimensions as the single inspired/expired ventilation pipe in figure 1 (both represent an alveolar ventilation of 4 litre min^{-1}); therefore, as drawn, this analogue would function in the same way as that in figure 1. However, the separate pipes make it possible to represent a difference between inspired and expired alveolar ventilations when the volume rate of uptake of anaesthetic from lungs to tissues becomes appreciable.

Results

THE CONSTANT-INFLOW CASE

If inspired ventilation is held constant, as is the case with most automatic lung ventilators, the width of the inspired ventilation pipe is fixed at that shown in figure 2; therefore, neglecting any small change in FRC, the width of the expired ventilation pipe must decrease. This is illustrated in figure 3A where the normal, pre-anaesthetic width of the expired ventilation pipe is indicated by a dotted line. Thus as the rate of removal of gas volume from the lungs by solution rapidly increases to its peak during induction, and then declines with approach to equilibrium, so the expired ventilation pipe must first contract to a corresponding extent, and then gradually re-expand to equal the inspired ventilation pipe in width when uptake ceases—very difficult to accomplish in an actual water analogue, but perfectly straightforward in a thought experiment.

Thus in this constant-inflow case, the inspired ventilation pipe in figure 3A remains the same width as that in figure 2, and hence the same as the common inspired–expired ventilation pipe of figure 1; therefore, inflow of anaesthetic to the lungs is the same in figure 3A as in figure 1. However, loss of anaesthetic in expired ventilation is less in figure 3A because of its narrowed expired ventilation pipe. Therefore, the alveolar concentration increases more rapidly (the lower water level (dotted ellipse) corresponds to that shown in fig. 1) and so does the rate of uptake from lungs to tissues; this leads to more rapid induction and a more rapid approach to equilibrium. Furthermore, the greater the inspired concentration, the greater the rate of uptake, the greater the narrowing of the expired ventilation pipe, the less the loss of anaesthetic and the faster the approach to equilibrium. The concentration effect is thereby reproduced in the water analogue.

THE CONSTANT-OUTFLOW CASE

If the expired ventilation is held constant (as a spontaneously breathing patient needs to do to maintain elimination of carbon dioxide, or as could be done by a ventilator with Servo control of the *expired* tidal volume) then it is the width of the expired ventilation pipe which is fixed at that shown in figure 2, while the inspired ventilation pipe progressively widens as the rate of uptake by solution increases to its peak (fig. 3B). Therefore, loss of anaesthetic in expired ventilation is the same in figure 3B as in figure 1, but the supply in the inspired ventilation is greater in figure 3B. Therefore, again, the alveolar concentration increases more rapidly, the rate of uptake into the tissues increases more rapidly and equilibrium is approached

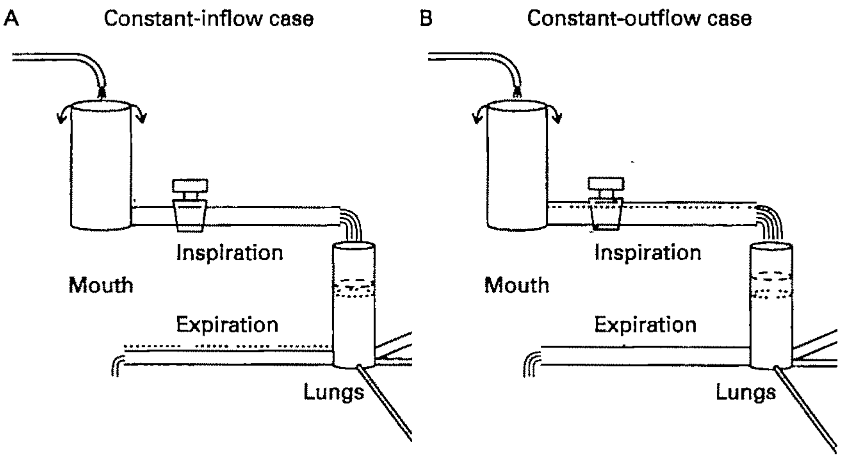

Figure 3 Two versions of the figure 2 analogue during the anaesthetic. The tissue containers have been omitted for compactness and clarity. A: constant-inflow case. The inspired alveolar ventilation has been fixed and is identical to that in figures 1 and 2 (4 litre min^{-1}); the expired alveolar ventilation has been reduced by the volume rate of uptake of nitrous oxide by solution; the dotted line indicates the normal, pre-anaesthetic width of the expiration pipe. B: constant-outflow case. The expired alveolar ventilation has been fixed, again identical to that in figures 1 and 2; the inspired alveolar ventilation has been increased by the volume rate of uptake; again, the dotted line indicates the normal width of the pipe. Both parts of the figure illustrate the conditions after 1 min of administration of 70% nitrous oxide when the rate of uptake by solution is near its peak (approximately 1 litre min^{-1}) so that in (A), the expired alveolar ventilation is 3 litre min^{-1} and in (B), the inspired alveolar ventilation is 5 litre min^{-1}. The difference in width between the inspired and expired ventilation pipes has been exaggerated deliberately to make it more obvious. Note that the water level in the lung container (upper, broken ellipse) is greater with constant outflow (B) than with constant inflow (A) and, in both cases, is greater than in figure 1 (lower, dotted ellipse) where the uptake by solution was ignored, which is permissible with low inspired concentrations. Rates of uptake and water levels (concentrations) were calculated using the computer model of figure 1 adapted to take account of the uptake by solution for each case.

more rapidly than in figure 1. Also, again, the greater the inspired concentration, the greater the rate of uptake; so here the greater the widening of the inspired ventilation pipe, the faster the approach to equilibrium. The concentration effect is thereby again reproduced.

In addition, the extra inflow of anaesthetic in this constant-outflow case is, for any given rate of uptake by solution, proportional to the *inspired* concentration, whereas the reduction in loss in the constant-inflow case is, again at any given rate of uptake, proportional to the *alveolar* concentration. Therefore, during induction (F_A less than F_I), at any given rate of uptake, the excess *net* inflow with the figure 3 model, over that of the figure 1 model, is greater in the constant-outflow case (fig. 3B) than in the constant-inflow case (fig. 3A). This in turn leads to a more rapid increase in alveolar concentration in the constant-outflow case and therefore there is an even greater net inflow than in the constant-inflow case. Thus as deduced from the enhanced rectangle diagram,[6] the concentration effect is more marked in the constant-outflow case than in the constant-inflow case. This is reflected in the higher level of water in the lung container in the constant-outflow case. (As in fig. 3A, the lower water level (dotted ellipse) corresponds to that in fig. 1.)

It is apparent that figure 2 incorporates the concentration effect into the water analogue in a simple manner: when the figure is used to simulate different inspired concentrations by making appropriate changes in the scaling factors, just as was done in changing from 1% to 70% nitrous oxide in relation to figure 1, no changes are required to the containers or to the blood flow pipes; it is sufficient to make the appropriate changes to one of the ventilation pipes as exemplified in figure 3.

THE SECOND-GAS EFFECT

When two agents are used simultaneously, two versions of the water analogue are required: each must be scaled according to the solubility in blood and tissues[7] of the agent represented, but both must be scaled also according to the physiological characteristics of the one patient—body mass, alveolar ventilation, and so on. In ventilation, the matter of solubility does not arise; therefore, the ventilation pipes are identical in the two analogues. Suppose that one agent is nitrous oxide at a high concentration and the other a volatile agent at low concentration. This is illustrated in figure 4 for the constant-inflow case, with isoflurane as the volatile anaesthetic. Although the inspired concentration of isoflurane would be much less than that of nitrous oxide, the same height has been used for both mouth containers. This simply implies the use of different appropriate scaling factors for the two analogues, as was done in making figures 1 and 2 represent 1% or 70% nitrous oxide. The water levels in the lung and tissue containers of each analogue represent the partial pressures there as fractions of the relevant inspired partial pressure.

In figure 4 the large volume rate of uptake of nitrous oxide has made the expired ventilation pipe of both analogues contract; therefore, there is less loss of the volatile anaesthetic than if it were present on its own. In the constant-outflow case (not illustrated) the inspired ventilation pipe of both analogues would be enlarged by the uptake of nitrous oxide; therefore, there would be a greater inflow of the volatile anaesthetic than if it were present on its own. Thus, in both cases, uptake of the volatile, the "second gas", is facilitated by the effect of the uptake of nitrous oxide on ventilation, that is, the water analogue of figure 2 allows the second-gas effect to be reproduced.

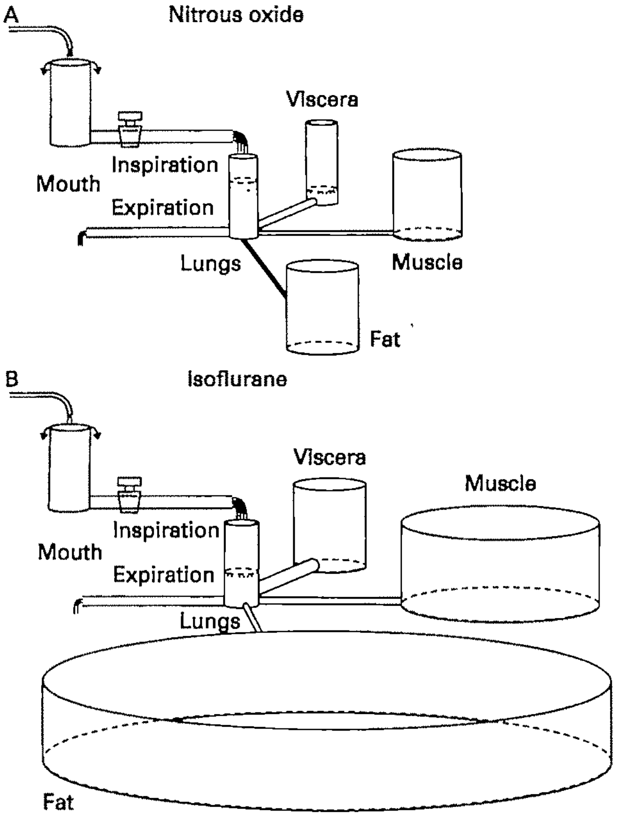

Figure 4 A pair of water analogues for the simultaneous administration of (A) nitrous oxide and (B) isoflurane. The conditions are assumed to be otherwise as in figure 3A (the constant-inflow case with alveolar ventilation=4 litre min^{-1} inspired, 3 litre min^{-1} expired). The concentration of isoflurane would be much less than that of nitrous oxide but, in accordance with custom,[7-9] the containers are the same height for both anaesthetics. This is because the height of each mouth container simply corresponds to the inspired concentration, and therefore to the inspired partial pressure, whatever that may be; and the water levels in the lung and tissue containers represent the partial pressures there as fractions of that inspired partial pressure. Note that the reduced expired alveolar ventilation (because of the large volume uptake of nitrous oxide) applies to the isoflurane analogue in addition to that for nitrous oxide. Therefore there is less loss of isoflurane in expired gas than there would be for isoflurane on its own, when the expired alveolar ventilation pipe would be the same width as the inspired one (as indicated by the dotted line). The figure illustrates the condition after 1 min of administration of 70% nitrous oxide plus 2% isoflurane; the lower, dotted ellipse in each container indicates the water level (partial pressure) which would exist if the inspired nitrous oxide concentration were only a few percent, that is with no concentration or second-gas effect.

Discussion

EFFECTS WITH OTHER ANAESTHETICS

In the argument above, the concentration and second-gas effects have been presented in terms of nitrous oxide. The effect still occurs with xenon and desflurane, but to a lesser extent. Xenon needs to be used in similar concentrations but has only one-third the solubility of nitrous oxide in blood[14 15]; desflurane has similar solubility[16] but is used at no more than one-quarter of the concentration. Historically, the effects were large with diethyl ether[17] because its very high solubility in blood, approximately 25 times that of nitrous oxide,[14] more than compensated for the lower concentrations used.

COMPARISON BETWEEN THE WATER-ANALOGUE-BASED AND RECTANGLE-DIAGRAM-BASED EXPLANATIONS

The above argument shows how the improved form of the water analogue in figure 2 leads, through figures 3 and 4, to an explanation of the concentration and second-gas effects; but how does this relate to the notably different approach[6] based on Stoelting and Eger's rectangle diagram?[5]

In reality, gas flows into the lungs continuously during all or most of the inspiratory phase of ventilation, and it flows out of the lungs continuously, usually during most or all of the expiratory phase. Meanwhile, during induction and maintenance of anaesthesia, uptake of inhaled anaesthetic by solution in blood flowing through the lungs occurs continuously throughout the whole of the respiratory cycle. Consequently, the inspired tidal volume is greater than the expired, and inspired ventilation is greater than expired ventilation. (Remember that "ventilation" is the inspiratory or expiratory flow averaged over the whole of the respiratory cycle.) It is this difference between inflow and outflow which leads to the concentration and second-gas effects.

The rectangle-diagram-based explanations of these effects have simplified this reality into a discrete, breath-by-breath model in which each breath is composed of four separate phases: inspiration (with no uptake); mixing of inspired gas with gas in the FRC (with no change in volume); uptake by blood (with contraction of lung volume but no inspiration or expiration); and expiration (with no uptake). Therefore, these explanations are in terms of *volumes*: tidal volumes and uptake volume per breath. The water analogue simplifies reality to the opposite extreme: inspiration, expiration and uptake into the blood are all continuous and simultaneous. Therefore, explanations of the concentration and second-gas effects are in terms of *flows*: inspired and expired ventilations and *rates* of uptake.

In rectangle-diagram-based explanations, the concentration and second-gas effects are seen to arise from the need to conserve volume: volume inspired equals volume taken up plus volume expired (plus or minus any decrease or increase in FRC, which is usually taken to be zero). In water-analogue-based explanations the effects are seen to arise from the need to conserve flow: inspired ventilation equals expired ventilation plus rate of uptake (plus or minus any rate of change in FRC).

The merit of the water analogue is that it provides something very close to a one-to-one correspondence between itself and the physiology of the body combined with the physicochemistry of the anaesthetic. Its limitation is that, in thought experiments, its predictions are only qualitative. The merit of the rectangle-based approach is that it can be quantitative—for a single breath, and given specified initial conditions. Its limitation is perhaps that it *has* to be presented in terms of numerical examples.

Perhaps the most striking difference in the detail of the two approaches is as follows. In the rectangle diagram, both effects are seen to arise from a *concentrating effect*. In the water analogue, the only circumstance where this would occur is in airway obstruction, or if the patient were assumed to be connected to a ventilator which forced the inspired and expired ventilations to be equal. In either case, uptake of nitrous oxide would result in a reduction in FRC which would be represented by the lung container shrinking laterally, thereby raising the level of the contained water. This would correspond to increasing the alveolar concentration of the anaesthetic represented—a concentrating effect.

ALTERNATIVE METHODS OF INCORPORATING THE CONCENTRATION AND SECOND-GAS EFFECTS IN THE WATER ANALOGUE

There has been one previous attempt at incorporating the concentration and second-gas effects into the water analogue.[8] This retained the common inspired–expired ventilation pipe but added a second mouth container and pipe above the main one, as in figure 5. For the constant-outflow case (fig. 5A) the head of water in the extra container is the same as in the main mouth container (corresponding to the inspired concentration); the extra pipe, which discharges into the lung container, represents only the flow of gas needed to compensate for the rate of gas-volume uptake by solution. Thus the pipe expands from zero width to a maximum as the rate of uptake increases to its peak, and then gradually contracts down towards zero as equilibrium is approached. Figure 5A is effective in specifically drawing attention to the extra inflow but it is a less direct representation of reality than figures 2 or 3.

For the constant-inflow case, it should be noted that figure 1 represents an expired ventilation equal to the inspired ventilation, whereas the former should be less than the latter by the rate of uptake by solution. The rate of loss of anaesthetic in expired ventilation is therefore too great in figure 1 by an amount equal to this volume rate of uptake multiplied by the *alveolar* concentration (as a fraction of an atmosphere). This excess loss is compensated in figure 5B by using an extra pipe to represent, as before, the rate of uptake by solution, but making the height of the extra mouth container correspond to the (continuously changing) *alveolar* concentration instead of to the inspired concentration.

The one merit of retaining the common ventilation pipe, and adding an additional rate-of-uptake pipe (with additional mouth container) is that the only apparent difference between the constant-inflow and constant-outflow cases is the height of water in the extra mouth container; this corresponds to the inspired concentration in the constant-outflow case (fig. 5A) and to the alveolar concentration in the constant-inflow case (fig. 5B). This makes it very clear that the concentration and second-gas effects are more marked in the constant-outflow case. However, this clarity is bought at the cost, in the constant-inflow case, of first grappling with the idea of over-representing loss in the expired ventilation and then compensating for that by an extra inflow of anaesthetic in an additional inspired-only ventilation.

To represent the second-gas effect by this alternative method would require a separate analogue for each agent, much as in figure 4. The blood-flow pipes and the tissue containers would be characteristic of each agent, but the common, inspired–expired ventilation pipe and the extra inflow pipe would be the same width for both agents. The extra inflow pipes would each represent the sum of the volume rates of uptake by solution of the two agents (here dominated by the uptake of nitrous oxide); each extra mouth container would have a height corresponding to the particular inspired or alveolar concentration for the constant-outflow and constant-inflow cases, respectively.

All the methods described so far for representing the concentration and second-gas effects in the water analogue involve continuously varying the width of

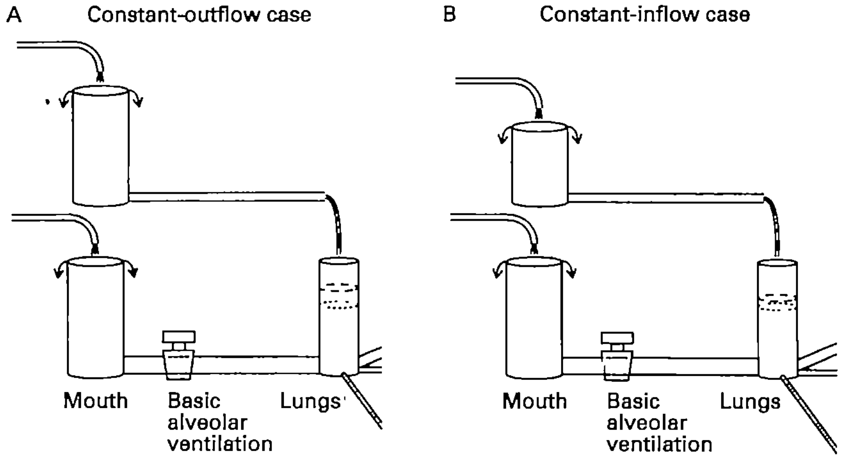

Figure 5 An alternative way of incorporating the concentration effect into the water analogue. A: Constant-outflow case. (Note the order of the cases has been removed compared with fig. 3.) The common alveolar ventilation pipe represents the initial, pre-anaesthetic alveolar ventilation (4 litre min^{-1}) as in the basic water analogue of figure 1; the additional narrow pipe represents the extra inspired-only alveolar ventilation needed to compensate for the rate of uptake by solution (approximately 1 litre min^{-1} at 1 min as in figures 3 and 4). The height of the additional overflowing container is the same as that of the mouth container, that is it corresponds to inspired concentration. This figure is similar to figure 3B except that the extra inspired alveolar ventilation is shown separately, instead of being accommodated by widening the separate inspired-ventilation pipe. B: Constant-inflow case. The features are similar to the constant-outflow case but the height of the extra overflowing container is now the same as the height of water in the lung container, that is it corresponds to alveolar concentration. The additional flow of water into the lung container, again approximately 1 litre min^{-1}, compensates for an excessive loss in the mouth–lung pipe (see text), which is prevented in figure 3A by a narrowing of the expired ventilation pipe. As in figures 3–4, the lower, dotted ellipses indicate the levels in the absence of the concentration effect.

one of the ventilation pipes in accordance with the varying rate of uptake by solution. This is perfectly satisfactory in a thought experiment, but impractical in a physical analogue. Before digital computers became available, there was a need to incorporate these effects in an electric analogue for the purpose of computation.[17 18] Then the problem was solved by showing that the concentration effect was mathematically equivalent to a reduction in solubility in blood and tissues, and by finding a practical method of implementing this when setting up the analogue for any particular computation.

Some such arrangement might be useful to *demonstrate* the effects in a physical water analogue but such a model would not aid the understanding of how the effects arise. However, in a computer graphics simulation of the water analogue, it would be perfectly practicable to incorporate the necessary continuous variation in the width of a ventilation pipe and in the water levels in the lung and tissue containers. This would simultaneously explain and demonstrate the concentration and second-gas effects.

We conclude that the water analogue is a valuable tool for teaching and the basic form (fig. 1) is adequate to explain most features of the pharmacokinetics of inhaled anaesthetics. When the concentration and second-gas effects are to be explained, one of the modifications described here is required. We believe that the version shown in figure 2, as elaborated in figures 3 and 4 (devised, and used for the past 10 yr, by one of us—W. W. M.), provides the most realistic and helpful explanation.

References

1. Eger EI II. A mathematical model of uptake and distribution. In: Papper EM, Kitz RJ, eds. *Uptake and Distribution of Anesthetic Agents.* New York: McGraw-Hill, 1963; 72–87
2. Eger EI II. Applications of a mathematical model of gas uptake. In: Papper EM, Kitz RJ, eds. *Uptake and Distribution of Anesthetic Agents.* New York: McGraw-Hill, 1963; 88–98.
3. Eger EI II. Effect of inspired anesthetic concentration on the rate of rise of alveolar concentration. *Anesthesiology* 1963; **24**: 153–157.
4. Epstein RM, Rackow H, Salanitre E, Wolf GL. Influence of the concentration effect on the uptake of anesthetic mixtures: the second gas effect. *Anesthesiology* 1964; **25**: 364–371.
5. Stoelting RK, Eger EI II. An additional explanation for the second gas effect: a concentrating effect. *Anesthesiology* 1969; **30**: 273–277.
6. Korman B, Mapleson WW. Concentration and second gas effects: can the accepted explanation be improved? *British Journal of Anaesthesia* 1997; **78**: 618–625 (erratum 1997, **79**: 268).
7. Mapleson WW. Absorption, distribution and excretion: kinetics. In: Chenoweth MB ed. *Modern Inhalation Anesthetics, vol. 30, Handbook of Experimental Pharmacology.* Berlin: Springer-Verlag, 1972; 326–344.
8. Mapleson WW. Pharmacokinetics of inhaled anaesthetics. In: Prys-Roberts C, Hug CC jr, eds. *Pharmacokinetics of Anaesthesia.* Oxford: Blackwell Scientific, 1984; 89–111
9. Mapleson WW. Pharmacokinetics of inhalational anaesthetics. In: Nunn JF, Utting JE, Brown BR jr, eds. *General Anaesthesia,* 5th Edn. London: Butterworths, 1989; 44–59.
10. Severinghaus JW. The rate of uptake of nitrous oxide in man. *Journal of Clinical Investigation* 1954; **33**: 1183–1189.
11. Smith WDA, Mapleson WW, Siebold K, Hargreaves MD, Clarke GM. Nitrous oxide anaesthesia induced at atmospheric and hyperbaric pressures. Part I: Measured pharmacokinetic and EEG data. *British Journal of Anaesthesia* 1974; **46**: 3–12.
12. Mapleson WW, Smith WDA, Siebold K, Hargreaves MD, Clarke GM. Nitrous oxide anaesthesia induced at atmospheric and hyperbaric pressures. Part II: Comparison of measured and theoretical pharmacokinetic data. *British Journal of Anaesthesia* 1974; **46**: 13–28.
13. Nunn JF. *Nunn's Applied Respiratory Physiology,* 4th Edn. Oxford: Butterworth-Heinemann, 1993; 393–394.
14. Steward A, Allott PR, Cowles AL, Mapleson WW Solubility coefficients for inhaled anaesthetics for water, oil and biological media. *British Journal of Anaesthesia* 1973, 45: 282–293.
15. Goto T, Suwa K, Uezono S, Ichinose F, Uchiyama M, Morita S. The blood-gas partition coefficient of xenon may be lower than generally accepted. *British Journal of Anaesthesia* 1998; **80**: 255–256.
16. Eger EI II. Partition coefficients of I-653 in human blood, saline, and olive oil. *Anesthesia and Analgesia* 1987, **66**: 971–973.
17. Mapleson WW. Inert gas-exchange theory using an electric analogue. *Journal of Applied Physiology* 1964; **19**: 1193–1199.
18. Mapleson WW. An electric analogue for uptake and exchange of inert gases and other agents. *Journal of Applied Physiology* 1963; **18**: 197–204.
19. Davis NR, Mapleson WW. Structure and quantification of a physiological model of the distribution of injected agents and inhaled anaesthetics. *British Journal of Anaesthesia* 1981; **53**: 399–405.
20. Mapleson WW. The theoretical ideal fresh-gas flow sequence at the start of low-flow anaesthesia. *Anaesthesia* 1998; **53**: 264–272.

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Comparison of the myocardial effects of desflurane and isoflurane in healthy patients: assessment by continuous oesophageal aortic blood flow echo-Doppler

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Summary

Experimentally, desflurane causes a moderate positive inotropic effect and a transient increase in arterial pressure with rapid increases in concentration compared with isoflurane. We used a continuous oesophageal aortic blood flow echo-Doppler device to study the myocardial effects of equi-anaesthetic concentrations of isoflurane and desflurane in 32 healthy patients undergoing superficial surgery. After induction of anaesthesia with midazolam, etomidate and fentanyl, general anaesthesia was maintained in 16 patients with 0.6% end-expired concentration of isoflurane and in 16 patients with 3% end-expired concentration of desflurane. Isoflurane induced a rapid decrease in aortic blood flow (ABF) which remained almost stable whereas desflurane induced an early, moderate and transient increase in ABF (1 min after introduction of the halogenated agent, mean ABF was 107 (SD 3)% in the desflurane group *vs* 95 (9)% in isoflurane group compared with control values before introduction of the inhalation agent; P=0.005), followed by a marked secondary decrease in ABF. The maximal decrease in ABF reached 71 (15)% of its initial value in the desflurane group compared with 80 (14)% in the isoflurane group (ns). Neither agent caused significant changes in other variables except for $P\text{E}'_{\text{CO}_2}$ which decreased in both groups. Continuous ABF echo-Doppler monitoring demonstrated an early transient positive inotropic effect of desflurane. (*Br. J. Anaesth.* 1998; **81**: 844–849).

Keywords: measurement techniques, blood flow; measurement techniques, echo-Doppler; anaesthetics volatile, desflurane; anaesthetics volatile, isoflurane; heart, myocardial function

Isoflurane and desflurane are inhalation anaesthetic agents which classically result in similar decreases in cardiac function.[1] However, desflurane may allow maintenance of higher mean arterial pressure by less decrease in systemic vascular resistance than isoflurane.[2,3] In contrast with isoflurane, rapid increase in desflurane concentration can increase heart rate and arterial pressure by sympathetic activation.[4–6] The precise mechanism of this sympathetic activation is not completely understood and may involve airway irritation by this pungent agent, transient disinhibition of centres modulating sympathetic efferent outflow, and/or peripheral action on sympathetic nerve endings.[7,8] A recent *in vitro* study suggested that in rat myocardium, desflurane induced a moderate positive inotropic effect compared with isoflurane.[9]

Experimental studies comparing the cardiovascular effects of isoflurane and desflurane are numerous but clinical investigations in healthy patients are not available. Invasive haemodynamic monitoring is necessary for such assessment, but is generally not indicated in common surgical procedures.

A non-invasive method using an aortic blood flow (ABF) ultrasound machine has previously proved reliable[12] and recently its value for anaesthetic monitoring has been documented.[13–15] Therefore, we conducted a clinical study to non-invasively compare haemodynamic changes induced by general anaesthesia with equi-anaesthetic concentrations of isoflurane or desflurane, using this new continuous oesophageal ABF echo-Doppler device.

Patients and methods

With the approval of the local Ethics Committee and after obtaining written informed consent, we studied 32 consecutive patients, aged 18–65 yr, ASA I, who suffered burns (burn surface area=1–30% of the total body surface area) and who required superficial surgical procedures. Patients undergoing surgery during the first 5 days after injury and those with an inhalation injury, sepsis or suspected oesophageal disease were excluded. The 32 patients were allocated randomly to receive either isoflurane or desflurane.

All patients were premedicated with hydroxyzine 100 mg and alprazolam 1 mg orally, 1 h before surgery. General anaesthesia was induced with midazolam 0.05 mg kg^{-1}, etomidate 0.4 mg kg^{-1} and fentanyl 3 µg kg^{-1} i.v. and neuromuscular block was achieved with vecuronium 0.1 mg kg^{-1}. After orotracheal intubation, the lungs were ventilated mechanically (tidal volume 12 ml kg^{-1}, ventilatory frequency 12 bpm) (Cato, Dräger, Lübeck, Germany). Anaesthesia was maintained initially by nitrous oxide (40% oxygen–60% nitrous oxide), and after the first

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haemodynamic measurements, by isoflurane or desflurane at equi-anaesthetic concentrations, using a rebreathing (semi-closed) system with soda lime as the carbon dioxide absorbent: the planned end-expired concentration (EEC) of isoflurane was 0.6% and desflurane, 3%.

After induction of anaesthesia, non-invasive continuous haemodynamic monitoring was performed with an oesophageal echo-Doppler aortic blood flowmeter (Dynemo 3000, Sometec Inc, Paris, France). Using continuous data provided by this device, an initial haemodynamic assessment was made after insertion of the probe, 5 min after the end of induction, and just before introduction of the halogenated agent (t_0). Thereafter, data were recorded at the following times: 1 min after the introduction of the halogenated agent (t_1); 5 min after the EEC of isoflurane reached a constant of 0.6% or of desflurane, 3% (t_2); 30 min after a constant EEC of halogenated anaesthetic (t_3); and just before the end of the isoflurane or desflurane inhalation period (t_4).

MEASUREMENT PRINCIPLE

By definition, the flow rate ($\dot{Q}$) passing through a cross-section of a blood vessel can be expressed as: $\dot{Q}=\mathrm{A}\times v$, where A=cross-section of the vessel and v=a spatial average velocity of blood over the entire cross-section. From the circular section of the thoracic aorta, the cross-sectional area can be calculated when the diameter is known ($\mathrm{A}=(\pi \mathrm{D}2)/4$). Velocity is measured using the Doppler formula: $v=[(C\times\Delta F)/(2\mathrm{Fe}\times\cos\Phi)]$, where C=ultrasound velocity inside the blood, ΔF=frequency variation of emitted ultrasounds, Fe=emission frequency and Φ=angle between the beam and the direction of blood motion. Determination of the real ABF requires simultaneous and continuous measurement of the aortic cross-section and of the blood velocity inside the aorta, at the same anatomical level where the aorta and oesophagus are nearly parallel. For the velocity measurement, the angle of incidence remains constant because a water-inflated balloon surrounding the transducers maintains the probe in a fixed position.

FLOWMETER AND PROBE

The flowmeter comprises three main parts: M-mode imaging system for continuous aortic diameter measurement, pulsed Doppler for descending aortic blood velocity measurement and a microprocessor system allowing flow calculations and integrating signals from peripheral devices to create a non-invasive haemodynamic profile.

The oesophageal probe has two ultrasound transducers. The first is a 10-MHz M-echo scanner with an emission narrow parallel beam of only 3 mm. It is located at the distal part of the probe perpendicular to the centre line. The second is a 5-MHz Doppler pulsed emission transducer mounted at an angle of 60° in relation to the centre line of the probe: the pulsed Doppler is emitted with a 20° divergent beam and the gate Doppler signal depth is adapted automatically to the diameter of the aorta. Divergence of ±20° of the Doppler beam allows insonation of the whole surface of the cross-section of the aorta. Insonation may be partial, if only part of the Doppler emission reaches the aortic target. To avoid errors from partial insonation of the aorta by the Doppler beam, the Dynemo 3000 uses an echographic orientation of the Doppler beam. Another error may occur if the negative systolic speed waves determined by blood cells moving back column does not occupy the whole section of the aorta. If the negative flow is calculated using the total aortic section, overestimation is systematically obtained. To avoid this problem, a proper balance of the diastolic velocity measurement, based on the detection of the residual energy of the Doppler signal, is used.

A cylindrical latex balloon is mounted on the sheath to be inflated with 8 ml of water. This inflated balloon maintains a constant angle of incidence of the ultrasound beams and allows the transducers to rotate freely without contact against the oesophageal mucosal wall. It ensures transmission of ultrasound waves without air interposition and dissipates any heat produced. The 10-MHz M-mode scan and the 5-MHz pulsed Doppler system allow very clear image resolution. The angle of incidence of the Doppler beam at 60° (complementary: 30°) was chosen to permit the Doppler ultrasound cut to be performed at the same level as the echographic cut over the descending aorta, allowing measurement of the diameter and blood velocity simultaneously at the same anatomical level.

HAEMODYNAMIC MONITORING

Just after induction of anaesthesia, the oesophageal ultrasonic probe was inserted and positioned. The depth of the probe in the oesophagus varied according to the height of the patient. The probe was first placed on the skin surface along the naso-oesophageal route and depth was measured on the probe between the echo transducer externally placed on the third intercostal juxtasternal space and a slide rubber ring placed at the level of the nose. The corresponding mark on the probe is a guide to depth limit. This distance corresponded to the approximate level where the aorta and oesophagus are parallel. The probe is then introduced into the oesophagus. Other monitoring devices are connected to the flowmeter: an oscillometric non-invasive sphygmomanometer which provided systolic and diastolic arterial pressure values; and an ECG (Propaq 104 EL, Protocol, Beaverton, USA).

The device calculates ABF, mean arterial pressure (MAP), heart rate (HR), stroke volume (obtained from the formula SV=ABF/HR) and systemic vascular resistance (SVR=MAP/ABF×79.9 whenever a new arterial pressure is provided). These two variables are indexed to ABF. Systolic time intervals (STI) were measured from the Q wave of the ECG signal and the acceleration signal was derived from the Doppler velocity signal. Opening and closing of the aortic valve were detected from the acceleration signal. The computer determined the duration of the pre-ejection period (PEP) between the Q wave and the beginning of the systolic acceleration front, corresponding to aortic valve opening. Starting at the end of PEP, left ventricular ejection time (LVET) was obtained by detecting the acceleration signal, the second maximum of systolic deceleration corresponding to aortic valve closure.[16] PEP and LVET were mea-

Table 1 Patient and operation characteristics (mean (SD) [range]). BSA=Burned surface area; Anaesthesia=duration of anaesthesia

Variable	Isoflurane group	Desflurane group
Age (yr)	36.4 [18–53]	34.6 [18–52]
Weight (kg)	68 (11) [52–85]	72 (9) [47–85]
Height (cm)	169 (9.5) [152–185]	172 (6.3) [157–180]
BSA (%)	13.3 (12.1) [1–30]	7.06 (5.8) [2–20]
Anaesthesia (min)	112.8 (72.8) [30–270]	83.6 (41.5) [45–230]

sured automatically and continuously and indexed to HR, according to the formula of Weissler, Harris and Schoenfeld.[17] PEP/LVET ratio was also calculated automatically. Monitoring of $P\text{E}'_{\text{CO}_2}$ (associated with measurement of the inspiratory and expiratory concentrations of the inhalation anaesthetics) by an infra-red analyser (Normocap 200, Datex, Helsinski, Finland) together with the haemodynamic profile provided simultaneous analysis of the variations in ABF and $P\text{E}'_{\text{CO}_2}$.[13 18 19] The haemodynamic values can be stored every 2 min (or at the operator's request) on floppy disc.

Results are expressed as mean (SD) or percentage of control values (t_0). Data were compared using Student *t* test. The effects of halogenated agents were compared using a repeated-measures analysis of variance (ANOVA) and the Newman–Keuls test. $P<0.05$ was considered statistically significant.

Results

Patient characteristics are shown in table 1. Thirty-two patients (27 males) were consecutively included: 16 received isoflurane and 16 desflurane. Mean age was 35 (range 18–53) yr and mean body surface area was 1.82 (SD 0.16) m^2.

There were no significant differences between groups but there was a trend towards a greater burned surface area and longer anaesthesia in the isoflurane group. The EEC of isoflurane and desflurane were relatively constant after induction (EEC=1.2 % and 4.5%, respectively, during induction, 0.7% and 3.1% at t_2, 0.7% and 2.9% at t_3 and 0.6% and 2.9% at t_4, respectively). Aortic diameter and ABF measurements were easily obtained in all patients. The quality of the aortic wall picture was excellent and diameter remained stable with less than 3% variation during the recordings (maximal recorded variation of the aortic diameter value for the same patient during the entire monitoring). No incident was noted with the device.

Table 2 shows the haemodynamic variations induced by isoflurane and desflurane. There were no significant changes in HR or MAP throughout the study in either group (fig. 1). $P\text{E}'_{\text{CO}_2}$ decreased moderately in both groups with a greater decrease in the desflurane group. In contrast, the other haemodynamic measurements showed variations during anaesthesia which differed between groups (fig. 2). One minute after introduction of the volatile anaesthetic agent, ABF and SV increased in the desflurane group and decreased in the isoflurane group: at t_1, ABF= 107 (3)% in the desflurane group compared with 95 (9)% in the isoflurane group ($P=0.005$) and SV=104 (7)% *vs* 96 (12)%, respectively ($P=0.04$). This difference persisted after constant equi-anaesthetic EEC for 5 min: at t_2, ABF=96 (9)% *vs* 80 (13)% ($P<0.0001$) and SV=97 (16)% *vs* 81 (18)% ($P=0.02$), respectively. Between t_2 and t_4, the decrease in ABF remained stable with isoflurane at 80 (14)% of its initial value at t_4, whereas ABF decreased at t_3 and t_4 with desflurane, reaching 71 (15)% of its initial value at t_4 ($P=0.08$) (fig. 2). The variations were comparable for SV and opposite for SVR, with a significantly higher value at t_2 in the

Table 2 Comparison of the haemodynamic variations induced by desflurane and isoflurane (mean (SD)) t_0=Before halogenated agent (control values); t_1=1 min after introduction of the agent; t_2=5 min after the EEC of isoflurane reached 0.6% or desflurane, 3%; t_3=after 30 min of inhalation of the anaesthetic agent; t_4=end of inhalation period. ABF=Aortic blood flow; MAP=mean arterial pressure; HR=heart rate; SV=stroke volume; SVR=systemic vascular resistance; PEPi=pre-ejection period indexed to HR; LVETi=left ventricular ejection time indexed to HR, $P\text{E}'_{\text{CO}_2}$=end tidal carbon dioxide pressure; $S\text{p}_{\text{O}_2}$=arterial hemoglobin saturation; EEC=end-expired concentration; Iso=isoflurane; Des=desflurane *$P<0.05$; **$P<0$ 001 *vs* baseline values (t_0) (ANOVA and Newman–Keuls test)

		t_0	t_1	t_2	t_3	t_4	P
ABF (litre min^{-1})	Iso	3,9 (1,2)	3,7 (1,2)	3,1 (1,0)**	3,0 (1,0)**	3,1 (0,9)**	
	Des	4,4 (1,3)	4,7 (1,4)	4,2 (1,4)	3,5 (1,2)**	3,1 (0,7)**	0 05
MAP (mm Hg)	Iso	84 (18)	82 (18)	79 (15)	78 (11)	80 (14)	
	Des	82 (16)	81 (13)	75 (16)	82 (15)	77 (10)	ns
HR (beat min^{-1})	Iso	80 (19)	79 (16)	79 (17)	75 (16)	76 (14)	
	Des	68 (16)	68 (13)	65 (9)	64 (7)	62 (9)	ns
SV (ml)	Iso	50 (19)	48 (15)	40 (11)*	41 (12)*	42 (15)*	
	Des	67 (27)	70 (26)	65 (21)	56 (20)*	50 (14)**	0 05
SVR (dyn s cm^{-5})	Iso	1831 (570)	1912 (654)	2228 (615)*	2240 (666)*	2252 (711)	
	Des	1633 (564)	1500 (486)	1576 (718)	2099 (802)*	2146 (607)**	0.05
PEPi (ms)	Iso	161 (16)	168 (14)	171 (18)	174 (24)	173 (23)	
	Des	166 (17)	173 (15)	181 (24)	187 (24)	196 (25)	ns
LVETi (ms)	Iso	404 (29)	403 (34)	404 (40)	393 (39)	391 (35)	
	Des	411 (31)	407 (28)	400 (21)	378 (27)	363 (25)*	0.05
PEP/LVET	Iso	0.40 (0.04)	0.42 (0.05)	0.43 (0.08)	0.45 (0.10)	0 45 (0.08)	
	Des	0.41 (0.06)	0.43 (0.05)	0.46 (0.07)	0.50 (0.07)*	0.54 (0.09)**	0.05
$P\text{E}'_{\text{CO}_2}$ (kPa)	Iso	4.5 (0.7)	4.4 (0.7)	4 4 (0.5)	4.3 (0.5)	4 3 (0.7)	
	Des	4.8 (0.7)	4.8 (0.8)	4.5 (0.7)	4.4 (0.7)	4.3 (0.5)*	0.05
$S\text{p}_{\text{O}_2}$ (%)	Iso	99 (1)	99 (1)	99 (1)	99 (1)	99 (1)	
	Des	99 (1)	99 (1)	98 (1)	99 (1)	99 (1)	ns
EEC (%)	Iso	0	1,2 (0,3)	0,7 (0,2)	0,7 (0,1)	0,6 (0,2)	
	Des	0	4,5 (0,5)	3,1 (0,5)	2,9 (0,3)	2,9 (0,2)	–
Aortic diameter (mm)	Iso	19.5 (2.9)	19.3 (2.7)	19.1 (2.9)	19.3 (2.9)	19.6 (2.9)	
	Des	20.6 (2.5)	20.6 (2.5)	20.5 (2.4)	20.6 (2.5)	20.8 (2.7)	ns

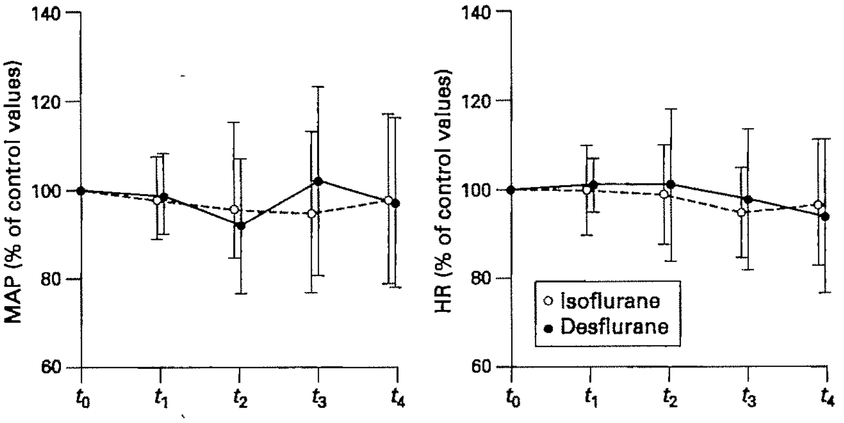

Figure 1 Changes in mean arterial pressure (MAP) and heart rate (HR) with desflurane and isoflurane, expressed as percentage of control values (t_0). Data are mean (SD). No significant differences.

isoflurane group (96 (17)% *vs* 122 (35)%, respectively; P=0.01) (fig. 2). PEPi gradually increased in both groups. LVETi decreased between t_1 and t_4 but more obviously in the desflurane group at t_4 (88 (7)% *vs* 97 (10) %, respectively; P=0.02). PEP/LVET ratio was significantly greater in the desflurane group compared with the isoflurane group at the end of the inhalation period (at t_4: 132 (22)% *vs* 112 (16)%, respectively; P=0.0003).

Discussion

Desflurane is a relatively new inhalation anaesthetic agent which differs from isoflurane only in the substitution of a fluorine for a chlorine atom,[20] with a lower blood solubility and a lower tissue–blood partition coefficient.[21] These characteristics indicate more rapid equilibration between tissues and blood and more precise control of alveolar anaesthetic concentration for desflurane.[21] Consequently, desflurane could be a useful agent, but its effects on the circulation have yet to be well established.

Comparisons between the cardiovascular effects of isoflurane and desflurane have been made for several years. Weiskopf and colleagues[22] and Merin and colleagues[2] studied the cardiovascular effects of desflurane in chronically instrumented swine or dogs, and showed that desflurane induced myocardial depressant effects which were similar to those produced by equi-anaesthetic concentrations of isoflurane. Pagel and co-workers[23] reported that desflurane induced less depression of myocardial contractility and less decrease in arterial pressure than isoflurane in chronically instrumented dogs. These differences were suppressed by autonomic nervous system block, suggesting that desflurane has a less depressant effect on autonomic activity.

Ebert and Muzi[4] reported that, in contrast with isoflurane, an increase in the vaporizer setting for desflurane from 1 to 1.5 MAC increased mean arterial pressure and muscle sympathetic nerve activity in human volunteers. Weiskopf and colleagues,[5] in a randomized clinical study, demonstrated that rapid increases in desflurane concentration to greater than 1 MAC caused transient sympathetic activation with increases in heart rate and arterial pressure. Sites mediating this sympathetic activation appeared to be located in the upper and lower airways, but the possibility of sites outside the airway must be considered.[7 8]

A recent *in vitro* study in isolated rat myocardium showed that desflurane induced a moderate positive inotropic effect compared with isoflurane.[9] This effect was related to intra-myocardial catecholamine release. Intra-myocardial catecholamine release could be one of the mechanisms participating in the sympathetic activation observed *in vivo* with desflurane.

In our study, whereas we did not observe any variation in HR or MAP, ABF and SV increased transiently in the desflurane group at the beginning of inhalation. This transient increase in ABF and SV with desflurane confirms the possible positive inotropic

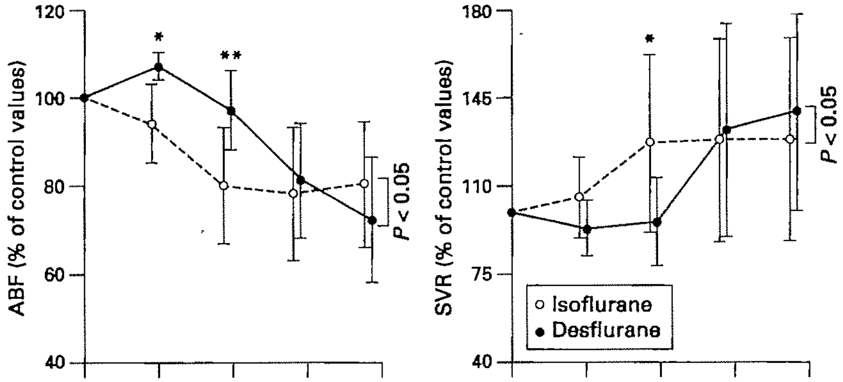

Figure 2 Changes in aortic blood flow (ABF) and systemic vascular resistance (SVR) with desflurane and isoflurane, expressed as percentage of control values (t_0). Data are mean (SD). *P<0.05, **P< 0.001 *vs* control values.

effects observed in isolated rat myocardium,[9] and also the sympathetic activation described during a rapid increase in desflurane inhalation.[5–7] We found a more marked decrease in ABF during maintenance of anaesthesia in the desflurane group. The lack of variation in MAP and HR could explain the increased SVR with isoflurane and desflurane during anaesthesia, but as SVR is calculated from ABF, the accuracy of this variable could be suspect. After the transient increase in ABF and SV in the desflurane group, we observed a consistent decrease in ABF, associated with an increase in PEP/LVET ratio in both groups. PEP/LVET ratio provides a simplified expression of alterations in STI, and thus the variations in PEP/LVET ratio reflect inotropic variables. In normal adults, this ratio averages 0.35 (0.05), and a PEP/LVET ratio increasing to 0.44 denotes decreased left ventricular performance.[24] Hence the longer term changes with both halogenated anaesthetic agents probably indicates a late decrease in myocardial contractility. The concomitant decrease in $P\text{E}'_{\text{CO}_2}$ can reflect impairment in tissue perfusion,[18 25] which could also be related to late alterations in cardiac performance, particularly in the desflurane group. Nevertheless, we cannot exclude the fact that the primary effects of these agents were on SVR and were unrelated to myocardial contractility. Unfortunately, because of rapid recovery with desflurane, we could not assess a reliable and comparable final measurement in both groups after the end of inhalation.

The main value of this study was the clinical conditions: usual premedication and induction of anaesthesia, maintenance of anaesthesia with halogenated agent associated with nitrous oxide in oxygen. All patients were ASA I and surgery was superficial and limited, and was unlikely to cause any haemodynamic changes. Thus our findings were attributed to the cardiovascular effects of the anaesthetic agents.

Nevertheless, several limitations have to be emphasized. First, the echo-Doppler ABF device gives an accurate assessment of aortic output but does not allow precise measurement of cardiac output. The main value of this system is measurement of trends in each variable during surgical and/or anaesthetic procedures. Even if the difficulties initially reported in the measurement of blood flow by ultrasound were solved,[26] thermodilution is a valuable and reliable technique (except for low cardiac output),[27] but remains discontinuous and invasive. In contrast, the ABF echo-Doppler device gives a continuous signal which provides haemodynamic assessment and trends in cardiovascular variables. The method correlates well with electromagnetic flow in animals[12 28] and with thermodilution in humans,[10 11] and the haemodynamic trends are useful in the assessment of various surgical procedures,[29 30] particularly variations induced by inhalation anaesthesia in adults[18 25] and in infants.[14 15] Second, MAP was not measured continuously. Transient variations in MAP may not have been recorded so that the accuracy of MAP and of the calculated SVR, is questionable. Third, a clinical study cannot distinguish primary myocardial or vascular effects of anaesthetic agents. Finally, the difference in the duration of anaesthesia could have interfered with t_4 values. Unfortunately, the clinical conditions of this study did not allow conclusions to be made from this late measurement.

In summary, our study has highlighted the value of continuous ABF echo-Doppler monitoring in the detection of moderate haemodynamic variations induced by halogenated anaesthetic agents in healthy patients. During desflurane inhalation, ABF increased transiently and then decreased, whereas during isoflurane inhalation, ABF first decreased and then remained almost stable. In both groups, the final decreases in ABF were 20–30% of their initial values. The concomitant and late increases in PEP/LVET ratio and decreases in $P\text{E}'_{\text{CO}_2}$ may also indicate slight impairment in tissue perfusion after prolonged halogenated inhalation, especially with desflurane. Such haemodynamic changes suggest caution when using desflurane in patients with hypertension or coronary artery disease.

Acknowledgement

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References

1. Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Influence of volatile anesthetics on myocardial contractility in vivo: desflurane versus isoflurane. *Anesthesiology* 1991; 74. 900–907.
2. Merin RG, Bernard JM, Doursot MF, Cohen M, Chelly JE. Comparison of the effects of isoflurane and desflurane on cardiovascular dynamics and regional blood flow in the chronically instrumented dog. *Anesthesiology* 1991; 74: 568–574
3. Weiskopf RB, Cahalan MK, Eger EI II, Yasuda N, Rampil IJ, Ionescu P, Lockhart SH, Johnson BH, Freire B, Kelley S. Cardiovascular actions of desflurane in normocarbic volunteers. *Anesthesia and Analgesia* 1991; 73: 143–156.
4. Ebert TJ, Muzi M. Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers. a comparison with isoflurane. *Anesthesiology* 1993; 79: 444–453.
5. Weiskopf RB, Moore MA, Eger EI II, Noorani M, McKay L, Chortkoff B, Hart PS, Damask M. Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. *Anesthesiology* 1994; 80: 1035–1045
6. Moore MA, Weiskopf RB, Eger EI II, Noorani M, McKay L, Damask M. Rapid 1% increases of end-tidal desflurane concentration to greater than 5% transiently increase heart rate and blood pressure in humans. *Anesthesiology* 1994; 81: 94–98.
7. Weiskopf RB, Eger EI II, Daniel M, Noorani M. Cardiovascular stimulation induced by rapid increases in desflurane concentration in humans results from activation of tracheopulmonary and systemic receptors. *Anesthesiology* 1995; 83: 1173–1178.
8. Muzi M, Ebert TJ, Hope WG, Robinson BJ, Belt LB Site(s) mediating sympathetic activation with desflurane. *Anesthesiology* 1996; 85: 737–747.
9. Gueugniaud PY, Hanouz JL, Vivien B, Lecarpentier Y, Coriat P, Riou B. Effects of desflurane in rat myocardium. Comparison with isoflurane and halothane *Anesthesiology* 1997; 87: 599–609.
10. Lavandier B, Cathignol D, Muchada R, Bui-Xuan B, Motin J. Noninvasive aortic blood flow measurement using an intraesophageal probe. *Ultrasound in Medicine and Biology* 1985; 11: 451–460.
11. Muchada R, Cathignol D, Lavandier B, Lamazou J, Haro D. Aortic blood flow measurement. *American Journal of Noninvasive Cardiology* 1988; 2. 24–31
12. Lavandier B, Muchada R, Chignier E, Fady JF, Birer A, Cathignol D. Assessment of a potentially noninvasive method for monitoring aortic blood flow in children. *Ultrasound in Medicine and Biology* 1991; 17: 107–116.
13. Gueugniaud PY, Bertin-Maghit M, Petit P, Muchada R. Diagnostic par surveillance du débit aortique et du capnogramme d'un arrêt circulatoire par embolie gazeuse au cours de la chirurgie laparoscopique. *Annales Françaises d'Anesthésie et de Réanimation* 1995; 14: 417–420.
14. Gueugniaud PY, Muchada R, Moussa M, Haro D, Petit P. Continuous oesophageal aortic blood flow echo-Doppler measurement during general anaesthesia in infants. *Canadian Journal of Anaesthesia* 1997; 44. 745–750.

15. Gueugniaud PY, Bertin-Maghit M, Abisseror M, Branche P, Piriou V, Bouchard C, Petit P. Myocardial effects of isoflurane in healthy infants and small children. Assessment by continuous oesophageal aortic blood flow echo-Doppler. *Acta Anaesthesiologica Scandinavica* 1998; **42**: 254–259.
16. Muchada R. Systolic time intervals. Experimental validation of a new measurement method. *Intensivmedizin* 1998; **34**: 26.
17. Weissler AM, Harris WS, Schoenfeld CD Systolic time intervals in heart failure in man. *Circulation* 1968; **37**: 149–156.
18. Tournadre JP, Moulaire V, Barreiro G, Brunel D, Van Straten V, Muchada R. Simultaneous monitoring of non invasive profile and capnography for tissue perfusion evaluation. *Journal of Anesthesia* 1994; **8**: 400–405.
19. Muchada R, Cathignol D. Oesophageal measurements of aortic blood flow by echo-Doppler. In: Vincent JL, eds. *Update in Intensive Care and Emergency Medicine*. Berlin: Springer Verlag, 1987; 356–365.
20. Eger EI II. Partition coefficients of I-653 in human blood, saline, and olive oil. *Anesthesia and Analgesia* 1987; **66**: 971–973.
21. Eger EI II. New inhaled anesthetics. *Anesthesiology* 1994; **80**: 906–922.
22. Weiskopf RB, Holmes MA, Eger EI II, Johnson BH, Rampil IJ, Brown JG. Cardiovascular effects of I-653 in swine. *Anesthesiology* 1988; **69**: 303–309.
23. Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Comparison of the systemic and coronary hemodynamic actions of desflurane, isoflurane, halothane, and enflurane in the chronically instrumented dog. *Anesthesiology* 1991; 74: 539–551.
24. Weissler AM. Current concepts in cardiology. Systolic time intervals. *New England Journal of Medicine* 1977; **296**: 321–324.
25. Brunel D, Muchada R. Evaluation de la perfusion tissulaire par surveillance simultanée du débit aortique et de la capnographie. *Presse Médicale* 1991; **20**: 1665–1666.
26. Evans DH. On the measurement of the mean velocity of blood flow over the cardiac cycle using Doppler ultrasound *Ultrasound in Medicine and Biology* 1985; **11**: 735–741.
27. Tournadre JP, Chassard D, Muchada R. Overestimation of low cardiac output measured by thermodilution. *British Journal of Anaesthesia* 1997; **79**: 514–516.
28. Muchada R, Rinaldi A, Cathignol D. Non invasive cardiovascular monitoring during general anaesthesia. *Minerva Anesthesiologica* 1990; **56**: 199–205.
29. Galimberti G, Berlot G, Muchada R, Gullo A. Haemodynamic changes during surgery in the knee-elbow position: a transoesophageal echo-Doppler study. *Anaesthesia* 1998; **53**: (Suppl. 2): 12–13.
30. Gueugniaud PY, Abisseror M, Moussa M, Godard J, Foussat C, Petit P, Dodat H. The hemodynamic effects of pneumoperitoneum during laparoscopic surgery in healthy infants. Assessment by continuous esophageal aortic blood flow Echo-Doppler. *Anesthesia and Analgesia* 1998; **86**: 290–293.

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Comparison of the effects of sevoflurane and isoflurane on arterial oxygenation during one lung ventilation

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Summary

We have compared the effects of sevoflurane and isoflurane on arterial oxygenation, heart rate and mean arterial pressure during one lung anaesthesia in a prospective, crossover study. We studied 28 patients undergoing oesophagogastrectomy, allocated alternately to one of two groups. Patients in group I/S (n=14) received 1 MAC (1.1%) of isoflurane in oxygen from induction until the end of 30 min of open chest one lung ventilation (OLV) in the lateral position. This was followed by 1 MAC (2.1%) of sevoflurane in oxygen for the next 30 min of OLV. Patients in group S/I (n=14) received the two anaesthetic agents in the reverse order. We found no significant difference in arterial oxygenation, heart rate or mean arterial pressure between the two potent inhalation agents. In the subgroup of patients with pulmonary artery catheters (n=12), we found a significant increase (P<0.05) in derived shunt during sevoflurane anaesthesia. There was no significant difference in mixed venous saturation and cardiac output. We conclude that during one lung ventilation, the choice between sevoflurane and isoflurane did not significantly influence arterial oxygenation. (*Br. J. Anaesth.* 1998; **81**: 850–853).

Keywords: anaesthetics volatile, sevoflurane; anaesthetics volatile, isoflurane; oxygen, partial pressure; ventilation, one lung; lung, shunting

One lung ventilation (OLV) is required for several thoracic operations. Adequate arterial oxygen is not achieved in some patients despite an accurately placed endobronchial tube and high inspired oxygen. Minor changes in arterial oxygen tension caused by changes in anaesthetic technique may be important in these patients. The effects of anaesthesia and OLV on arterial oxygenation are complex and not fully understood. Potent inhalation agents are used widely for thoracic anaesthesia; they have several desirable properties, including ease of administration, rapid onset and offset, and ability to cause bronchodilatation. One potential drawback is inhibition of hypoxic pulmonary vasoconstriction (HPV).

Isoflurane has been shown previously to be superior to both halothane and enflurane with respect to arterial oxygenation during one lung anaesthesia.[1 2] Sevoflurane has some advantages over isoflurane. Its non-pungent odour facilitates smooth and rapid gaseous induction[3 4] and its lower blood-gas partition coefficient results in faster recovery from anaesthesia.[5–9] Rapid emergence from anaesthesia is important after some thoracic procedures, for example lung reduction surgery. *In vitro*, sevoflurane inhibits hypoxic pulmonary vasoconstriction in a dose-related manner similar to isoflurane.[10] Acceptable arterial oxygenation was achieved during one lung ventilation in sheep anaesthetized with sevoflurane.[11] The purpose of this study was to compare the effects of sevoflurane and isoflurane on arterial oxygenation, heart rate and mean arterial pressure during one lung anaesthesia. In a subgroup of patients, we also compared mixed venous saturation, derived shunt and cardiac output.

Patients and methods

This prospective crossover study was approved by the Liverpool Research Ethics Committee. Informed written consent was obtained from adult patients undergoing oesophagogastrectomy. Exclusion criteria were previous lung resection and contraindications to epidural analgesia. Patients were allocated alternately to one of two groups.

Baseline heart rate, arterial pressure and spirometry were recorded on the day before operation. Patients were premedicated with diazepam 0.15 mg kg^{-1}. On arrival in the anaesthetic room, 10 ml kg^{-1} of i.v. fluid were given over 20 min followed by infusion of 10 ml kg^{-1} h^{-1}. A radial arterial cannula and a mid-thoracic epidural catheter were inserted under local anaesthesia. No epidural test dose was given. An arterial blood-gas sample during air breathing was obtained before induction of anaesthesia. After preoxygenation, general anaesthesia was induced with fentanyl 1.5 µg kg^{-1} and propofol 2–3 mg kg^{-1}. Neuromuscular block was achieved with vecuronium, followed by intubation with a left double-lumen endobronchial tube (Rusch, Kernen, Germany). Correct tube position was confirmed with a fibreoptic bronchoscope.

Patients assigned to group I/S received 1 MAC (1.1%) of end-tidal isoflurane in oxygen from induction until the end of the first 30 min of open chest OLV in the lateral position. They then received 1 MAC (2.1%) of end-tidal sevoflurane in oxygen for the next 30 min of OLV. During the changeover, fresh gas flow 6 litre min^{-1} was used to facilitate washout of the previous anaesthetic agent and washin of the new anaesthetic agent. Patients

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assigned to group S/I received the two inhalation agents in reverse order.

A pulmonary artery catheter (Baxter, Edwards Critical-Care Division, Irvine, CA, USA) was inserted in those patients undergoing left thoracotomy and who had consented to this additional monitoring. In all patients other monitoring included: ECG, pulse oximetry, nasopharyngeal temperature, neuromuscular block, ventilation pressures and volumes (Cato, Drager, Lubeck, Germany), end-tidal carbon dioxide concentration and anaesthetic gases by infrared spectroscopy (Cato, Drager, Lubeck, Germany). After the patient was placed in the semi-lateral position (45° tilt from the horizontal), a forced-air warming blanket (Bair Hugger, Augustine Medical, Inc; Eden Prairie, MN, USA) was placed on the lower extremities. Pressure transducers (Omeda, Herts, UK) were zeroed at the mid-vertebral line.

All patients received an epidural bolus dose of fentanyl 1 $\mu g\ kg^{-1}$ followed by an infusion of 1 $\mu g\ kg^{-1}\ h^{-1}$ during the study. Motor block of more than 80% was maintained with incremental doses of vecuronium. During OLV, tidal volume was set initially at 10 ml kg^{-1} and reduced if required to maintain peak inspiratory pressure of less than 30 cm H_2O. The I:E ratio was set at 1:2 and ventilatory frequency was adjusted to maintain arterial carbon dioxide tension at 4.7–5.9 kPa. Before the onset of OLV, the position of the double-lumen endobronchial tube was rechecked with the aid of a fibreoptic bronchoscope. Collapse of the non-dependent lung was confirmed by direct observation. Intraoperative arterial pressure was maintained within 20% of baseline measurement with i.v. fluid or i.v. fentanyl as required.

Intraoperative haemodynamic (Tram 600, Marquette Electronics, Inc; Milwaukee, WI, USA) and blood-gas measurements (IL1640 BGElectrolytes Analyser and CO-Oximeter, Barcelona, Spain) were obtained at the end of each 30-min period of OLV by the same observer who was not blinded to the anaesthetic used. Cardiac output was measured using the thermodilution technique. Derived shunt and oxygen consumption were calculated using standard formulae. Shunt equation:[12]

$$Qs/Qt=(Cc'_{O_2}-Ca_{O_2})/(Cc'_{O_2}-C\bar{v}_{O_2})$$

where Cc'_{O_2}=pulmonary capillary blood oxygen content assuming 100% saturation of capillary blood; Ca_{O_2}=arterial blood oxygen content; and $C\bar{v}_{O_2}$=mixed venous blood oxygen content.

Power analysis was performed using a mean difference in Pa_{O_2} of greater than 3 kPa as clinically significant and an estimated SD of the differences of 5.4 kPa. To detect this mean difference with 80% power at the 5% level of significance, we needed to recruit 27 patients.

Results are given as mean (SD). Statistical analysis was performed in accordance with the simple crossover design methodology.[13]

Treatment effect (isoflurane *vs* sevoflurane) was sought under the expectation that there were no treatment effects. Thus we compared treatment effect using the null hypothesis: $(Iso_{group\ I/S}-Sevo_{group\ I/S})=(Sevo_{group\ S/I}-Iso_{group\ S/I})$. Period (transfer) effect was sought under the expectation that there was no period effect. Thus period effect was analysed using the null hypothesis: $(Iso_{group\ I/S}-Sevo_{group\ I/S})=(Iso_{group\ S/I}-Sevo_{group\ S/I})$, where Iso=variables measured at the end of 30 min OLV with 1 MAC of isoflurane and Sevo=variables measured at the end of 30 min OLV with 1 MAC of sevoflurane.

Table 1 Preoperative data for all patients (mean (SD or range) or number). No significant difference between groups

	Group I/S (n=14)	Group S/I (n=14)
Sex (M/F)	9/5	9/5
ASA (II/III)	6/8	5/9
Age (yr)	64 (50–73)	63 (53–78)
Weight (kg)	72 (14)	67 (13)
Height (cm)	170 (7.6)	168 (10.6)
Preoperative FEV_1 (% of predicted)	95 (16)	80 (24)
Preoperative FVC (% of predicted)	102 (13)	92 (18)
Preoperative Pa_{CO_2} (kPa)	5.3 (0.4)	5.2 (0.42)
Preoperative Pa_{O_2} (kPa)	10.7 (1.2)	10.5 (1.1)
Heart rate (beat min^{-1})	76 (15.2)	79 (10.8)
Mean arterial pressure (mm Hg)	100 (8.6)	98 (9.2)

Student's *t* test was used for evaluation of differences within and between groups. For all tests, the level of significance was set at 5%.

Results

We studied 28 patients; 14 patients were allocated alternately to each group. Table 1 summarizes the preoperative data of group I/S and group S/I. There was no significant difference in preoperative data between the two groups.

Six patients in each group had a pulmonary artery catheter inserted. Twenty-five of the 28 patients had a left thoracotomy. One patient in group I/S and two patients in group S/I had a right thoracotomy. One patient in each group received additional i.v. fentanyl at the start of operation during initial two lung ventilations. No patient required additional i.v. fluid. There was a significant decrease in mean arterial pressure during OLV with sevoflurane and isoflurane in both groups compared with preoperative values. Table 2 summarizes the intraoperative data of group I/S and group S/I.

In the comparison between sevoflurane and isoflurane treatment effect, there was no significant difference in arterial oxygenation, heart rate or mean arterial pressure. In the subgroup of patients with pulmonary artery catheters, there was a significant increase in derived shunt during sevoflurane anaesthesia compared with isoflurane. There was no significant difference in mixed venous saturation or cardiac output. No significant period effect was demonstrated for arterial oxygenation, heart rate or mean arterial pressure. In patients with pulmonary artery catheters, a significant period effect was found only in mixed venous saturation (table 3).

Discussion

Patients undergoing oesophagogastrectomy were studied because this operation allowed at least 1 h of OLV with minimal trauma to the non-dependent lung. We chose 30 min as the duration before the changeover of anaesthetic agent. This was based on previous human studies which showed that Pa_{O_2}

Table 2 Intraoperative data at the end of each 30 min of OLV with 1 MAC of each anaesthetic agent (mean (SD)). HR=Heart rate, MAP=mean arterial pressure, MPAP=mean pulmonary artery pressure, CO=cardiac output, SVR=systemic vascular resistance, Sv_{O_2}=mixed venous oxygen saturation, *Qs/Qt*=pulmonary shunt flow. *$P<0.05$ compared with preoperative values

	Group I/S (n=14)		Group S/I (n=14)	
	Isoflurane	Sevoflurane	Sevoflurane	Isoflurane
HR (beat min^{-1})	84 (8.4)	81 (9.4)	86 (10.6)	85 (10.9)
MAP (mm Hg)	75 (7.3)*	75 (6.1)*	76 (5.8)*	79 (8.2)*
Pa_{O_2} (kPa)	21.2 (11.8)	23.4 (17)	26 1 (14.6)	30.1 (18.2)
	Group I/S (n=6)		Group S/I (n=6)	
	Isoflurane	Sevoflurane	Sevoflurane	Isoflurane
MPAP (mm Hg)	19.7 (3.1)	20.3 (3.2)	22.5 (4.5)	21.7 (4.3)
CO (litre min^{-1})	6.8 (2)	6.4 (1.4)	5.9 (1.5)	5.8 (1.5)
SVR (dyn s cm^{-5})	791 (282)	850 (236)	906 (274)	1051(356)
Sv_{O_2} (%)	80 (4.2)	77 (4 9)	78 (8.5)	75 (8)
Qs/Qt (%)	43 (4)	44 (4)	39 (12)	35 (8)
O_2 consumption (ml min^{-1})	190 (34)	187 (49)	181 (30)	209 (24)

Table 3 Comparison of treatment effect (isoflurane *vs* sevoflurane) and analysis of period effect (mean (SD)). HR=Heart rate, MAP=mean arterial pressure, MPAP=mean pulmonary artery pressure, CO=cardiac output, SVR=systemic vascular resistance, Sv_{O_2}=mixed venous O_2 saturation, *Qs/Qt*=pulmonary shunt flow, Iso=variables measured at the end of 30 min OLV with 1 MAC of isoflurane, Sevo=variables measured at the end of 30 min OLV with 1 MAC of sevoflurane. *$P<0.05$ for treatment effect: ($\text{Iso}_{\text{group I/S}}-\text{Sevo}_{\text{group I/S}}$) *vs* ($\text{Sevo}_{\text{group S/I}}-\text{Iso}_{\text{group S/I}}$); †$P<0.05$ for period effect: ($\text{Iso}_{\text{group I/S}}-\text{Sevo}_{\text{group I/S}}$) *vs* ($\text{Iso}_{\text{group S/I}}-\text{Sevo}_{\text{group S/I}}$)

	Group I/S (n=14) Iso–Sevo	Group S/I (n=14) Sevo–Iso	Group S/I (n=14) Iso–Sevo
HR (beat min^{-1})	3.07 (5.99)	1.36 (5.44)	–1.36 (5.44)
MAP (mm Hg)	–0.14 (6.42)	–2.79 (8.47)	2.79 (8.47)
Pa_{O_2} (kPa)	–2.17 (9.97)	–4.01 (11.24)	4.01 (11.24)
	Group I/S (n=6) Iso–Sevo	Group S/I (n=6) Sevo–Iso	Group S/I (n=6) Iso–Sevo
MPAP (mm Hg)	–0.67 (2.94)	0.83 (1.83)	–0.83 (1.83)
CO (litre min^{-1})	0.43 (1.3)	0.15 (0.39)	–0.15 (0.39)
SVR (dyn s cm^{-5})	–59 (142)	–145 (175)	145 (175)
Sv_{O_2} (%)	2 37 (2.6)	3.15 (4.5)	–3.15 (4.5)†
Qs/Qt (%)	–1 (1.8)	4.1 (4.7)*	–4.1 (4.7)
O_2 consumption (ml min^{-1})	3.23 (33.4)	–27.6 (14.6)	27.6 (14.6)

stabilized as early as 20 min after initiation of OLV.[12 14] The initial washout of inhalation agent was rapid, but low concentrations persisted for several hours which can potentially exert a biological effect. This raises the question of period effect in this study, which used a crossover design. This important issue was not dealt with in previous crossover studies investigating oxygenation during OLV.[2 14] In this study we demonstrated no significant period effect in the outcome variables of arterial oxygenation, heart rate or mean arterial pressure. We found a significant period effect in the subgroup of patients with pulmonary artery catheters for mixed venous saturation. A longer duration between the changeover of anaesthetic agents and sampling might have avoided a period effect. We had to balance this against the time constraint of a clinical study.

A left double-lumen endobronchial tube was used for all patients to minimize the risk of tube displacement. We do not routinely insert pulmonary artery catheters in patients undergoing oesophagogastrectomy. To gain approval from the Ethics Committee, we agreed not to measure pulmonary artery occlusion pressure and to minimize the number of patients with a pulmonary artery catheter. We did not know in advance how many of the 27 patients required for this study would consent to insertion of a pulmonary artery catheter. We alternately allocated our patients in order to ensure an equal distribution of patients with a pulmonary catheter between the two groups. This method is unlikely to bias the outcome in this study as the same surgeon (R. D. P.) performed all surgery and the same anaesthetist (J. Y. Y. W.) gave all anaesthetics. Further, only one oesophagogastrectomy was performed at each operating session and there was no regular pattern to the scheduling of cases. Finally, we found no significant difference in preoperative data between the two groups.

During OLV, adequate oxygenation can be a concern, especially in the supine position and in patients with poor pre-existing lung function. Therefore, it is important for anaesthetists to be aware of all the variables which can influence oxygenation. Arterial oxygenation (Pa_{O_2}) is determined by pulmonary capillary oxygenation (Pc_{O_2}), mixed venous oxygenation ($P\bar{v}_{O_2}$) and shunt. Pc_{O_2} depends on PA_{O_2} and therefore inspired oxygen and ventilation. $P\bar{v}_{O_2}$ depends on tissue oxygen delivery, and therefore cardiac output (*Qt*), and oxygen consumption. Shunt blood flow through the atelectatic lung during OLV depends principally on HPV, rather than the mechanical effects of lung collapse.[15] HPV is a function of both PA_{O_2} and $P\bar{v}_{O_2}$.[16] General anaesthetic agents can affect Pa_{O_2} by two possible mechanisms. First, they can alter $P\bar{v}_{O_2}$ by altering *Qt*; second, they can alter shunt flow directly by inhibition of HPV and indirectly by altering HPV through a change in $P\bar{v}_{O_2}$.

In vitro, i.v. anaesthetic agents do not directly inhibit hypoxic pulmonary vasoconstriction while potent inhalation agents, such as halothane, enflurane, isoflurane and sevoflurane, directly inhibit HPV in a dose-related manner to a similar degree.[10,17,18] *In vivo*, this direct inhibitory effect on shunt and Pa_{O_2} is more difficult to demonstrate as haemodynamic effects of the general anaesthetic agents can also influence these variables. In human studies, comparing i.v. anaesthetic agents with inhalation anaesthetic agents during OLV, 1 MAC of halothane caused a slight but significant increase in shunt and a decrease in Pa_{O_2}, up to 2 MAC of enflurane caused no significant change in shunt or Pa_{O_2} and 1 MAC of isoflurane caused no significant change in shunt or Pa_{O_2}.[1,19] In a study comparing isoflurane with enflurane during OLV, Pa_{O_2} and $P\bar{v}_{O_2}$ were found to be significantly higher during isoflurane anaesthesia; there was no significant difference in shunt or oxygen consumption, and the authors postulated that the difference in oxygenation may be explained by better preservation of *Qt* that occurred during isoflurane anaesthesia.[2] Total i.v. anaesthesia with propofol infusion is a widely accepted technique. Propofol infusions in the range of 6–12 mg kg^{-1} h^{-1} do not inhibit HPV.[20] When isoflurane was compared with propofol–alfentanil, there was no significant difference in Pa_{O_2}.[14] A separate study comparing isoflurane and propofol anaesthesia showed a significant increase in shunt and cardiac output during isoflurane anaesthesia.[21] The increase in *Qt* during isoflurane anaesthesia could explain why there was no difference in Pa_{O_2} despite the increase in shunt.

Inhalation anaesthesia is generally favoured over i.v. anaesthesia for surgery requiring OLV because it has several advantages. These include ease of drug delivery, offset independent of hepatic or renal function, end-tidal concentration monitoring, bronchodilatation and the option of gaseous induction. Sevoflurane is a relatively new anaesthetic agent with some advantages over isoflurane. A non-pungent odour allows rapid and smooth inhalation induction without the arrhythmogenic potential of halothane.[3,4] A lower blood-gas partition coefficient allows more rapid onset, easier titration and most importantly faster recovery from anaesthesia.[5–9] Earlier recovery of spontaneous respiration and cough reflexes can potentially benefit the thoracic patient. In our study, there was no difference in Pa_{O_2}, heart rate or mean arterial pressure between sevoflurane and isoflurane. In patients with pulmonary artery catheters, there was a significant increase in derived shunt during sevoflurane anaesthesia. There was no significant difference in $P\bar{v}_{O_2}$ or cardiac output. These results are not unexpected as the two drugs inhibit HPV in a similar dose–response manner *in vitro* and have a similar cardiovascular profile with the possible exception of a lower heart rate with sevoflurane.[7–9,22,23] The combined dose of i.v. and epidural fentanyl given in this study could have masked any difference in heart rate between isoflurane and sevoflurane.[23]

Combining data from the two groups gave an average shunt of 39% for isoflurane. This is consistent with three previous studies in which the inspired oxygen was 100%. Shunt during OLV in these studies were 38%, 39% and 41%.[1,2,14]

In summary, there was no significant difference in arterial oxygenation in patients anaesthetized with sevoflurane or isoflurane in the semi-lateral position during OLV. As sevoflurane offers some advantages over currently used potent inhalation agents, its suitability for thoracic anaesthesia warrants further evaluation.

References

1. Benumof JL, Augustine SD, Gibbons JA. Halothane and isoflurane only slightly impair arterial oxygenation during one-lung ventilation in patients undergoing thoracotomy *Anesthesiology* 87; 67: 910–915.
2. Slinger P, Scott WAC. Arterial oxygenation during one-lung ventilation. A comparison of enflurane and isoflurane *Anesthesiology* 1995; 82: 940–946
3. Yurino M, Kimura H. Comparison of induction time and characteristics between sevoflurane and sevoflurane/nitrous oxide. *Acta Anaesthesiologica Scandinavica* 1995, 39. 356–358
4. Yurino M, Kimura H Induction of anesthesia with sevoflurane, nitrous oxide and oxygen. A comparison of spontaneous ventilation and vital capacity rapid inhalation induction techniques. *Anesthesia and Analgesia* 1993; 76: 598–601.
5. Eger E. New inhaled anesthetics *Anesthesiology* 1994; 80 906–922.
6. Smith I, Ding Y, White PF. Comparison of induction, maintenance and recovery characteristics of sevoflurane–N$_2$O and propofol–sevoflurane–N$_2$O with propofol–isoflurane–N$_2$O anesthesia *Anesthesia and Analgesia* 1992; 74: 253–259
7. Philip BK, Kallar SK, Bogetz MS, Scheller MS, Wetchler BV A multicenter comparison of maintenance and recovery with sevoflurane or isoflurane for adult ambulatory anesthesia *Anesthesia and Analgesia* 1996; 83: 314–319.
8. Frink EJ, Malan TP, Atlas M, Dominguez LM, DiNardo JA, Brown B. Clinical comparison of sevoflurane and isoflurane in healthy patients *Anesthesia and Analgesia* 1992; 74: 241–245
9. Campbell C, Nahrwold ML, Miller DD. Clinical comparison of sevoflurane and isoflurane when administered with nitrous oxide for surgical procedures of intermediate duration. *Canadian Journal of Anaesthesia* 1995, 42: 884–890.
10. Ishibe Y, Gui X, Uno H, Shiokawa Y, Umeda T, Suekane K. Effect of sevoflurane on hypoxic pulmonary vasoconstriction in the perfused rabbit lung. *Anesthesiology* 1993, 79. 1348–1353
11. Fugita Y, Yamasaki T, Takaori M, Sekioka K. Sevoflurane anaesthesia for one-lung ventilation with PEEP to the dependent lung in sheep. *Canadian Journal of Anaesthesia* 1993, 40. 1195–1200.
12. Nunn JF. *Applied Respiratory Physiology*, 3rd Edn Boston Butterworths, 1987, 167–176
13. Armitage P, Berry G. The simple crossover design. In. *Statistical Methods in Medical Research.* Oxford: Blackwell, 1987, 222–223
14. Reid CW, Slinger PD, Lenis S. A comparison of the effects of propofol–alfentanil versus isoflurane anesthesia on arterial oxygenation during one-lung ventilation *Journal of Cardiothoracic Anesthesia* 1996; 10. 860–863
15. Miller FL, Chen L, Malmkvist G, Marshall C, Marshall BE. Mechanical factors do not influence blood flow distribution in atelectasis. *Anesthesiology* 1989; 70: 481–488.
16. Marshall C, Marshall BE Site and sensitivity for stimulation of hypoxic pulmonary vasoconstriction. *Journal of Applied Physiology* 1983; 55: 711–716
17. Bjertnaes LJ. Hypoxic-induced vasoconstriction in isolated perfused lungs exposed to injectable or inhalational anaesthetics. *Acta Anaesthesiologica Scandinavica* 1977; 21: 133–147
18. Marshall C, Lindgren L, Marshall BE. Effects of halothane, enflurane, and isoflurane on hypoxic pulmonary vasoconstriction in rat lungs *in vitro*. *Anesthesiology* 1984; 60: 304–308.
19. Carlsson AJ, Hedenstierna G, Bindslev L Hypoxic-induced vasoconstriction in human lung exposed to enflurane anaesthesia. *Acta Anaesthesiologica Scandinavica* 1987; 31: 57–62
20. Keer LV, Aken HV, Vandermeersch E, Vermaut G, Lerut T. Propofol does not inhibit hypoxic pulmonary vasoconstriction in humans. *Journal of Clinical Anesthesia* 1989; 1: 284–288
21. Kellow NH, Scott AD, White SA, Feneck RO. Comparison of the effects of propofol and isoflurane anaesthesia on right ventricular function and shunt fraction during thoracic surgery *British Journal of Anaesthesia* 1995, 75: 578–582.
22. Malan TP, DiNardo JA, Isner RJ, Frink EJ, Goldberg M, Fenster PE, Brown EA, Depa R, Hammond LC, Mata H. Cardiovascular effects of sevoflurane compared with those of isoflurane in volunteers. *Anesthesiology* 1995, 83: 918–928
23. Ebert TJ, Harkin CP, Muzi M. Cardiovascular responses to sevoflurane: A review. *Anesthesia and Analgesia* 1995; 81. S11–22

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Propofol infusion for induction and maintenance of anaesthesia in patients with end-stage renal disease

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Summary

We have investigated the pharmacokinetics and pharmacodynamics of propofol in 11 patients with end-stage renal disease (ESRD) compared with nine healthy patients during and after a manually controlled three-stage infusion of propofol 21, 12 and 6 mg kg^{-1} h^{-1} lasting a minimum of 2 h. Mean total body clearance was not reduced significantly in the ESRD group (30.66 (SD 8.47) ml kg^{-1} min^{-1}) compared with the control group (33.75 (7.8) ml kg^{-1} min^{-1}). ESRD patients exhibited a greater, but not statistically significant, volume of distribution at steady state compared with patients in the control group (11.25 (8.86) *vs* 5.79 (2.14) litre kg^{-1}, respectively). Elimination half-life values were unchanged by renal failure. Mean times to induction of anaesthesia were similar in both groups: 177 (SD 57) and 167 (58) s for the ESRD and control groups, respectively. Waking time after cessation of propofol infusion was significantly shorter in the ESRD group (474 (156) s) compared with the control group (714 (240) s) ($P<0.05$). Mean plasma concentrations on waking were similar. We conclude that the pharmacokinetic and pharmacodynamic profiles of propofol after infusion were not markedly affected by renal failure. (*Br. J. Anaesth.* 1998; **81**: 854–860).

Keywords: anaesthetics i.v., propofol; anaesthetic techniques, i.v. infusion; kidney, failure; pharmacokinetics, propofol

Selection of a safe and effective drug regimen for patients with renal impairment can be difficult. Data obtained from studies in subjects with normal renal function cannot with confidence be used to design a drug administration regimen for patients with end-stage renal disease (ESRD). Renal failure may influence hepatic drug metabolism either by inducing or inhibiting hepatic enzymes and also by altering protein binding or protein denaturation.[1 2] Drug disposition may be affected by changes in body fluid distribution and circulatory volume in these dialysed patients. This can induce changes in hepatic blood flow which in turn can alter production and elimination of metabolites.[1]

Propofol is used widely as an i.v. anaesthetic agent for both induction and maintenance of general anaesthesia. In healthy patients, propofol has a relatively large volume of distribution and a high total body clearance.[3–5] The drug is extensively biotransformed in the liver and its metabolites appear to have no pharmacological activity.[6] Since the first report of Morcos and Payne on the disposition of a bolus dose of propofol in four patients with chronic renal failure,[7] Kirvelä and colleagues have concluded that propofol may be used safely for induction of general anaesthesia in patients with renal impairment.[8] Limited information has been obtained on the use of a continuous infusion of propofol in patients with renal impairment for maintenance of general anaesthesia.[9]

We have investigated the safety of propofol infusion for induction and maintenance of anaesthesia in uraemic patients, and whether or not its pharmacokinetics and pharmacodynamics were similar in a group of healthy patients anaesthetized in a similar way.

Patients and methods

The study was approved by the Institutional Ethics Committee of the University Hospital and all patients gave informed consent. We enrolled 11 patients, ASA III or IV, with creatinine clearance rates of less than 10 ml min^{-1}, presenting for arteriovenous fistulae surgery (ESRD group) and 10 patients, ASA I, with normal renal function (group C) undergoing surgery of an expected duration of at least 120 min. These patients did not suffer from cardiac or hepatic dysfunction or obesity (body weight not exceeding 20% of ideal). Patients' characteristics and laboratory data are summarized in table 1. Concurrent therapy was received only by patients in the ESRD group (table 2). No patient was receiving cytochrome P450 inducers or inhibitors.

All patients were premedicated with diazepam 10 mg orally, 1 h before anaesthesia, except for one patient in the ESRD group who received bromazepam. Electrocardiogram, arterial pressure (by sphygmomanometry measured on a lower limb in the ESRD group) and oxygen saturation (by pulse oximetry) were monitored continuously. Before

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Table 1 Patient characteristics and preoperative laboratory values (mean (SD)). NR=Normal range

	Control	ESRD	*P*
Age (yr)	45.2	45.1	ns
Height(cm)	171.6 (10)	164 (5.7)	ns
Weight (kg)	72.6 (10)	62.3 (7.9)	0.01
Sex (M/F)	4/5	5/6	ns
Haemoglobin (g litre^{-1}) (NR 13–17.7)	14.2 (1.6)	9.9 (2)	<0.01
Creatinine (mg dl^{-1}) (NR 0.2–1.2)	0.86 (0.12)	17.6 (25.8)	<0.01
Albumin (g dl^{-1}) (NR 3.5–5)	4.38 (0.61)	3.71 (0.53)	<0.05
AST (iu litre^{-1}) (NR 5–35)	16 (4)	14 (7)	ns
ALT (iu litre^{-1}) (NR 5–35)	16 (5)	15 (10)	ns
Creatinine clearance (ml min^{-1}) (NR 70–120)	102.8 (20)	7.3 (3.3)	<0.01

Table 2 Antihypertensive medication received by patients in the ESRD group

Patient No.	Medication
1	Metoprolol
2	—
3	—
4	Atenolol
5	—
6	Amiodarone
7	Nifedipine, Metoprolol
8	Nifedipine, Metoprolol
9	—
10	Metoprolol
11	Metoprolol

induction of anaesthesia, a venous catheter was inserted in the contralateral arm to that undergoing surgery, for infusion of 5% dextrose at a rate of 3 ml kg^{-1} h^{-1} and for drug administration until the end of anaesthesia. A catheter was also inserted into the radial artery of the same arm for blood sampling and continuous monitoring of arterial pressure. The lungs were preoxygenated with 100% oxygen and after administration of fentanyl 0.1 mg i.v., anaesthesia was induced and maintained using a three-step infusion regimen of propofol, delivered by a calibrated syringe pump (Ohmeda): 21 mg kg^{-1} h^{-1} for 5 min, followed by 12 mg kg^{-1} h^{-1} for 10 min and 6 mg kg^{-1} h^{-1} until the end of the procedure. The final rate was not altered throughout the study and no supplementary doses were given. A bolus dose of vecuronium 0.1 mg kg^{-1} was given at loss of consciousness to facilitate tracheal intubation. Ventilation was maintained with 60% nitrous oxide in oxygen and end-tidal carbon dioxide concentration was kept constant at 4–4.5 kPa by adjusting ventilation. Bolus doses of fentanyl 0.05 mg were administered when heart rate or mean arterial pressure increased to more than 30% of preoperative values. If arterial pressure decreased by more than 20% of mean pressure, ephedrine 5 mg i.v. was administered. Dextran 70 000, 6% up to a maximum of 200 ml, was given to ESRD patients at the surgeon's request. The propofol infusion was maintained for at least 120 min according to the length of the procedure, and duration of infusion was noted. At the end of the surgical procedure, neuromuscular block was antagonized when four twitches of the train-of-four response were present at the adductor pollicis muscle. Nitrous oxide was stopped simultaneously with the propofol infusion.

CLINICAL ASSESSMENT

Time to induction of anaesthesia was defined as the time from the beginning of infusion of propofol to the absence of response on verbal stimulation. Recovery was assessed by measurement of the time from the end of infusion to when patients opened their eyes and answered standard questions correctly. The total amount of fentanyl was noted as was the time since the last dose to cessation of the infusion and amount of ephedrine and additional fluids given.

PHARMACOKINETICS

Arterial blood samples (2 ml) for measurement of propofol concentrations in whole blood were obtained before induction of anaesthesia and at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 21, 25, 30, 40, 50, 60, 75, 105 and 120 min after initiation of infusion. For infusions continuing beyond 120 min, additional samples were collected every 15 min. After cessation of infusion, further samples were collected at 2, 4, 6, 8, 10, 20, 40, 60, 90, 120, 240, 300, 360, 420, 480 and 720 min. Additional samples were obtained when patients lost consciousness and when they opened their eyes to verbal command. Samples were cooled immediately and stored at +4°C, and assays were carried out within 12 weeks. Whole blood concentrations of propofol were measured by high pressure liquid chromatography (HPLC) with fluorescence detection.[10] The assay had an inter-batch coefficient of variation of 3–12% with a limit of detection of 0.002 µg ml^{-1}. As a quality control, 20% of all sample assays were replicated in a separate batch; differences between assay results were less than 10%. Bi- and triexponential functions of the following form, derived from Colburn,[11] were fitted to the data using the least squares curve fitting program MKMODEL (Holford N. MKMODEL Version 3.36 User Manual, Biosoft, Cambridge, UK, 1988):

$$
\begin{aligned}
C_t = {} & 3.5 * \sum_{i=1}^{2\text{ or }3} C_i * (1-e^{-\lambda_i * T_1}) * e^{-\lambda_i * (t-5)} \\
& +2.0 * \sum_{i=1}^{2\text{ or }3} C_i * (1-e^{-\lambda_i * T_2}) * e^{-\lambda_i * (t-15)} \\
& +1.0 * \sum_{i=1}^{2\text{ or }3} C_i * (1-e^{-\lambda_i * T_3}) * e^{-\lambda_i * (t-T)}
\end{aligned}
$$

where C_t=propofol concentration at any time t after the start of the first infusion; γ_1, γ_2 and γ_3=model fitted hybrid rate constants for three exponential phases; these are referred to as α, β and γ, respectively, in the tabulation and reporting of results. $T=T_1+T_2+T_3$; T_1, T_2 and T_3=times from the start of each infusion to the maximum times for that infusion; t=total time from the start of the first infusion. When (t–5), (t–15) or (t–T) is not greater than 0, then that function is set to zero. C_1, C_2 and C_3=model-fitted coefficients defining the contribution to the steady state concentration of each exponential phase; 3.5, 2.0 and 1.0=ratios of the three infusion rates to the terminal infusion rate (6 mg kg^{-1} h^{-1}). In all non-linear least squares analysis it is necessary to weight the dependent variable (concentration) data in such a way that the weighted errors for this variable are constant over the full range of the independent variable; these errors include contributions from both the assay and inter-subject variability.[12] Balant and Garrett justify this by showing that the use of equal weights can virtually ignore terminal phase data, if the data range over two or more logarithmic cycles.[12] In our study a weighting of $1/C^2$ was used for all data sets. This was confirmed as optimal in a subset of patients; residuals for observed data points from the line of best fit indicated a better fit when using a weighting factor of $1/C^2$ compared with $1/C$.

The following parameters were derived from the fitted model:

$$\text{Steady state propofol concentration } (C^{ss}) = \sum_{i=1}^{2\text{ or }3} C_i$$

$$\text{Total body clearance } Cl(\text{m}) = \text{terminal infusion rate}/C^{ss}$$

$$\begin{pmatrix}\text{Volume of central} \\ \text{compartment } (V_1)^3\end{pmatrix} = \text{total dose}/ \sum_{i=1}^{2\text{ or }3} C_{i\,\text{corr}}$$

where C_i corr.=fitted coefficients corrected for the infusion duration using the method described by Loo and Riegelman.[13]

$$\begin{pmatrix}\text{Apparent volume of} \\ \text{distribution at equilibrium } (V^{\gamma})\end{pmatrix} = Cl\text{m}/\gamma$$

Model-independent parameter estimates were calculated to validate the parameters derived from the fitted model and were as follows:

$$\text{Total body clearance } Cl(\text{mi}) = \text{total dose}/\text{AUC}_{\infty}$$

where AUC_{∞}=area under the propofol concentration curve extrapolated to infinity, calculated using the trapezoidal approximation:

$$\begin{pmatrix}\text{Apparent volume of} \\ \text{distribution at} \\ \text{steady state } (V^{ss})\end{pmatrix} = \frac{\text{AUMC}_{\infty} \times \text{total dose}}{(\text{AUC}_{\infty})^2} - \frac{\text{total dose} \times \text{infusion duration}}{2 \times (\text{AUC}_{\infty})}$$

where AUMC_{∞}=area under the first moment of the propofol concentration curve extrapolated to infinity, calculated using the trapezoidal approximation.

$$\text{Mean residence time MRT} = \text{AUMC}_{\infty}/\text{AUC}_{\infty}$$

STATISTICAL ANALYSIS

The number of patients required to detect a predefined difference in a pharmacokinetic parameter between groups was estimated from data in a previous study.[7] Total body clearance was considered to be the most important variable on which to base calculations. We considered it clinically important to detect a 30% reduction in control mean. With 10 patients per group and a significance level of 5%, the power of the study was estimated as 75% using a standard statistical method.[14] All data are expressed as mean (SD). The data were analysed by the Wilcoxon rank sum test for between-group comparisons of pharmacokinetic data and measured data. *P* values were calculated using PC-SAS version 6.04 computer program (SAS Institute Inc., Cary, NC, USA, 1990). $P<0.05$ was considered significant. Inter-subject variability difference between groups was tested for the pharmacokinetic data using the *F* test of Snedecor (SAS/STAT User's Guide, Release 6.03 Edition. Cary, NC: SAS Institute Inc., 1988). Mean arterial pressure and heart rate from induction to 60 min after infusion of propofol between the two groups were compared by analysis of variance (ANOVA) for repeated measurements using the multivariate approach with the pre-induction value in the contrast statement.

Results

For the control group, surgery consisted of lumbar hernia (four patients), varicose vein surgery (two patients), mastectomy (one patient), rhinoplasty (two patients) and laparoscopy (one patient). Anaesthesia was uneventful in all patients except for one in the control group. In this patient, anaesthesia was continuously too light as a result of technical problems with the infusion pump and all data from this patient were excluded from analysis. Mean body weight in the ESRD group was significantly smaller than that in the control group but there was no significant difference between groups for age or height (table 1). Patients in the ESRD group had been haemodialysed within the previous 24 h.

Discomfort at the injection site was reported by one patient in each group. Mean duration of infusion was 176 (SD 60) min (range 120–315 min) for the ESRD group and 152 (48) min (120–250 min) for the control group (ns). Patients lost consciousness within 177 (57) s and 167 (58) s after the beginning of infusion in the ESRD and control groups, respectively (ns). The corresponding mean propofol concentration in the ESRD group (4.41 (1.93) μg ml^{-1}) was higher than that in the control group (3.71 (1.14) μg ml^{-1}). This difference was not statistically significant. Patients with impaired renal function opened their eyes significantly earlier than control patients (474 (156) s compared with 714 (240) s, respectively) ($P<0.05$). Blood propofol concentrations on awakening were not significantly different (0.89 (0.43) and 0.78 (0.33) μg ml^{-1} in the ESRD and control groups, respectively).

Mean time at which patients were able to answer questions correctly was significantly shorter in the ESRD group (978 (258) s) than in the control group (1266 (198) s) ($P<0.05$). The total amount of fentanyl administered was larger in the control group (0.317 (0.178) mg) than in the ESRD group (0.215 (0.085) mg). However, this difference was not significant. Time from the last fentanyl dose before termination of the propofol infusion (59 (26) *vs* 64 (21) min in the control and ESRD groups, respectively) was not significantly different between groups. No major haemodynamic instability was detected in either group.

A mean volume of 223 (69) ml of Dextran 70 000, 6% was infused in nine patients in the ESRD group. Two patients in both groups received ephedrine (up to a total of 20 mg for each patient in the ESRD group). In the control group, one patient received ephedrine 5 mg and one 10 mg. Heart rate did not differ between groups except at 10 and 60 min after induction of anaesthesia. There was no difference between groups in mean arterial pressure.

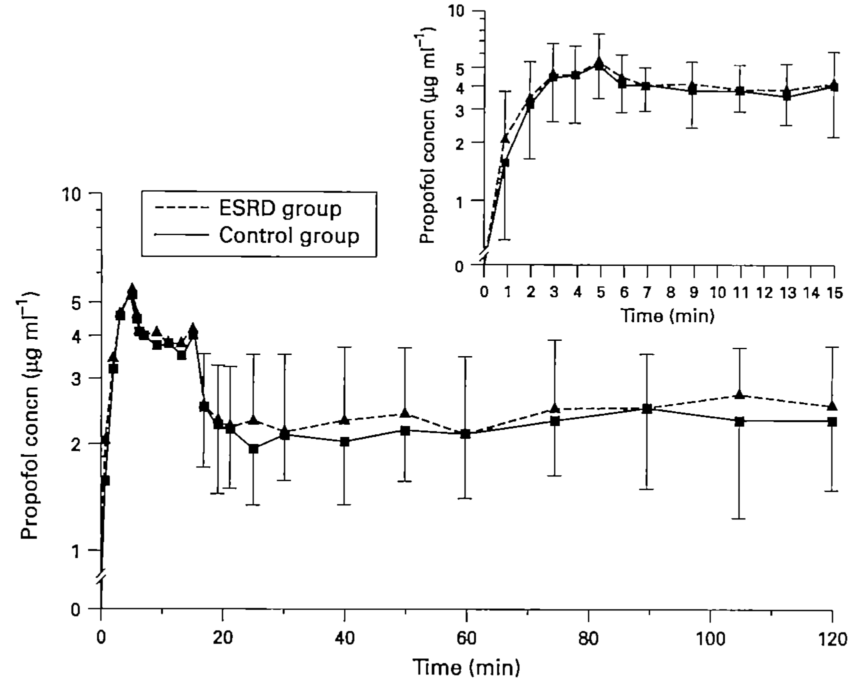

Figure 1 Mean (SD) blood concentrations of propofol (logarithmic scale) during infusion of propofol in the end-stage renal failure (ESRD) and control groups In the right corner of the graph (inset), the first 15 min after the beginning of the infusion are magnified

PHARMACOKINETICS

Changes in mean blood concentration of propofol with time, during and after infusion, followed a similar pattern in both groups (figs 1, 2). After an initial peak concentration of 5 µg ml^{-1} at 5 min after the start of infusion, the profile reflected the changes in infusion rate; changes in mean concentration from 12 min onwards were small (fig. 1). After termination of the infusion, propofol concentrations declined curvilinearly with time (fig. 2). Two- and three-compartment models were fitted to the full propofol concentration profile for each patient. These were compared by reference to the Schwarz criterion and by inspection of the residuals of the observed data from the line of best fit.[15] For three patients in each group, the preferred model was two compartment as three phases could not be defined with confidence.

Individual values for the pharmacokinetic parameters are shown in table 3 for both model-dependent and model-independent analyses. To eliminate bias cause by the patient's weight, the appropriate pharmacokinetic data were analysed with adjustment for body weight. Estimates of propofol clearance were similar for both analyses. There was no significant difference between ESRD and control patients for any of the pharmacokinetic parameters. The F test of Snedecor showed no inter-subject variability difference between the groups tested for clearance but there was a significant difference in variability for the volumes of distribution (table 3).

Discussion

Clearance of propofol is predominantly metabolic as little or no unchanged propofol is detected in excreta[16]; this emphasizes the importance of the liver in the clearance of propofol.[3–5, 17] In patients with renal failure, hepatic drug metabolism may be increased, decreased or remain unchanged.[1, 2] Our study has confirmed that uraemia requiring haemodialysis does not affect significantly the pharmacokinetics of propofol. Mean clearance in the renal failure patients (30.6 ml min^{-1} kg^{-1}) was similar to that of healthy control patients (33.8 ml min^{-1} kg^{-1}), whether derived by model or model-independent analysis. Moreover, mean clearance in the ESRD group was similar to that reported in other healthy patient groups receiving propofol as an infusion (23.8–28.3 ml min^{-1} kg^{-1}).[3, 18, 19] This indicates that the infusion dose requirements of propofol in ESRD patients are similar to those in patients with normal renal function. Extrahepatic mechanisms for clearance of propofol have been thought to explain values in excess of the total blood supply to the liver.[7, 20, 21] The fact that there was no significant reduction in total body clearance in the ESRD group in this study suggests that clearance by the kidney, if present in humans, is not contributing significantly to the clearance of propofol. It is interesting to note that the sheep kidney has been observed to convert a metabolite of propofol (probably propofol glucuronide) into propofol[22]; data from our study suggest that this is unlikely to occur in humans. The medications received by the ESRD group did not appear to influence the pharmacokinetics of propofol.

The volume of the central compartment, V_1, was similar in the two groups (0.13 (0.067) *vs* 0.12 (0.039) litre kg^{-1} for the ESRD and control groups, respectively) but was at the lower end of the range reported previously (0.12–0.42 litre kg^{-1}).[3, 18, 19] This probably resulted from a combination of the high frequency of sampling during the early period of the infusion[23] and the use of arterial blood. Arterial blood sampling was chosen in this study because it is considered to be the most appropriate when performing pharmacokinetic modelling and pharmacodynamic assessments.[24, 25]

Plasma expansion fluids were given in the ESRD group but not in the control group. However, the

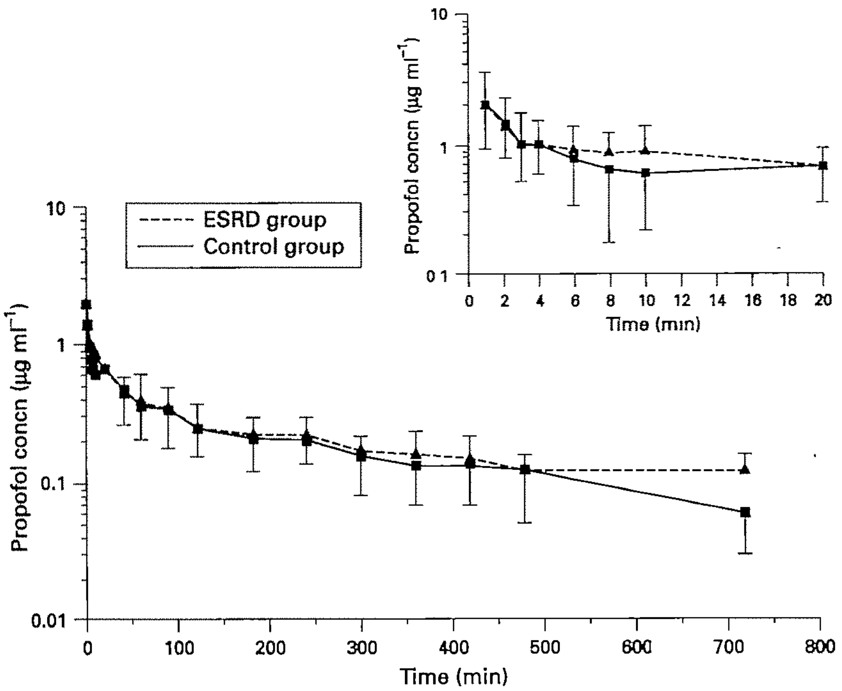

Figure 2 Mean (SD) blood concentrations of propofol (logarithmic scale) after infusion of propofol in the end-stage renal failure (ESRD) and control groups. In the right corner of the graph (inset), the first 20 min after infusion cessation are magnified.

amounts given were small in these chronically haemodialysed patients with restricted fluid intake and it is considered that the difference would be unlikely to affect the volume of distribution substantially, as intravascular volume is only a small part of the volume of distribution of propofol.

The mean value for V^{ss} in our control patients (5.8 litre kg^{-1}) was somewhat higher than that reported in other studies of propofol infusions with a similar sampling duration (1.8–3.6 litre kg^{-1}).[18,19,26,27] The mean value for V^{ss} in the ESRD group (11.3 litre kg^{-1}) was higher than that in the control group

Table 3 Individual pharmacokinetic data from the model and from model-independent analysis. $T_{1/2}^{\alpha}$, $T_{1/2}^{\beta}$, $T_{1/2}^{\gamma}$=initial, intermediate and terminal half-lives, respectively; C^{ss}=propofol concentration at steady state; V_1 kg^{-1}=volume of distribution of the central compartment per kg body weight; V^{γ} kg^{-1}=volume of distribution at equilibrium per kg body weight; *Cl*(m) kg^{-1} and *Cl*(mi) kg^{-1}=total body clearance per kg body weight derived, respectively, from model-dependent and model-independent analysis; V^{ss} kg^{-1}=volume of distribution at steady state per kg body weight; MRT=mean residence time. *P* values for the Wilcoxon rank sum test for between-group comparison and for the *F* test of Snedecor

Patient No.	$T_{1/2}^{\alpha}$ (min)	$T_{1/2}^{\beta}$ (min)	$T_{1/2}^{\gamma}$ (min)	C^{ss} (μg ml^{-1})	V_1 kg^{-1} (litre kg^{-1})	V^{γ} kg^{-1} (litre kg^{-1})	*Cl*(m) kg^{-1} (ml kg^{-1} min^{-1})	*Cl*(mi) kg^{-1} (ml kg^{-1} min^{-1})	V^{ss} kg^{-1} (litre kg^{-1})	MRT (min)
Control										
1	1.69	27.9	554	3.92	0.10	20.4	25.4	25.4	5.43	317
2	1.10	23.7	408	2.48	0.09	23.7	40.3	38.5	4.11	167
3	0.83	37.3	282	3.04	0.10	13.4	33.0	31.8	4.52	209
4	1.16	—	243	2.11	0.17	16.6	47.4	50.1	10.61	272
5	0.90	—	212	2.84	0.07	10.8	35.2	32.5	4.26	191
6	1.12	25.8	447	2.93	0.13	22.1	34.2	32.0	4.82	275
7	1.59	17.4	541	4.43	0.12	17.6	22.5	23.8	8.04	397
8	1.71	34.3	420	3.65	0.10	16.6	27.4	26.2	5.24	260
9	2.41	—	491	2.61	0.20	27.2	38.3	41.4	5.15	212
Median	1.16	26.9		2.93	0.10	17.6	34.2	32.0	5.15	260
Mean	1.39	27.7		3.11	0.12	18.7	33.8	33.5	5.79	256
SD	0.50	7.2		0.74	0.04	5.1	7.8	8.5	2.14	71
ESRD										
1	1.36	37.3	525	4.31	0.10	17.6	23.2	20.9	4.71	382
2	0.97	17.6	396	5.53	0.06	10.3	18.0	17.7	2.61	208
3	2.48	17.5	283	3.62	0.26	11.3	27.7	25.8	3.53	201
4	0.68	19.5	554	3.44	0.05	23.2	29.0	28.0	4.59	266
5	1.48	25.5	513	4.06	0.09	18.2	24.6	23.4	4.06	259
6	1.01	24.9	839	2.35	0.16	51.6	42.6	41.6	22.86	657
7	0.81	—	398	2.35	0.10	24.5	42.5	44.0	15.39	441
8	2.32	—	499	3.42	0.17	21.0	29.2	30.6	11.77	448
9	1.18	27.9	550	2.36	0.16	33.6	42.3	60.5	17.42	378
10	0.65	20.4	491	3.94	0.08	18.0	25.3	24.0	8.00	393
11	1.65	—	813	3.06	0.22	38.4	32.7	35.5	28.91	828
Median	1.18	22.7		3.44	0.10	21.0	29.0	28.0	8.00	382
Mean	1.32	23.8		3.49	0.13	24.3	30.6	32.0	11.25	406
SD	0.61	6.7		0.97	0.07	12.4	8.5	12.6	8.86	192
P	ns	ns		ns	ns	ns	ns	ns	ns	ns
F test	ns	ns		ns	ns	0.02	ns	ns	0.002	ns

(5.8 litre kg^{-1}). This difference was not statistically significant, possibly as a consequence of the significantly larger inter-subject variability in the ESRD group (*F* test of Snedecor). V^{γ}, V^{ss} and the terminal half-life values for propofol in our study were smaller than those observed previously in patients with chronic renal failure.[8 9] This may be because of the longer sampling period after administration of propofol (24 h)[28] or the sampling site used.[25] Chiou has pointed out that profiles of concentration in blood or plasma from different sampling sites can lead to calculation of widely differing pharmacokinetic parameters and that venous concentration data may grossly misrepresent the true distributive and terminal phases of a drug in the body.[25] The total sampling duration was clearly inadequate to define $T_{1/2}{}^{\gamma}$ with confidence in all subjects; it has been suggested that estimated values of this half-life tend to increase with sampling duration[28] and this is consistent with the very long $T_{1/2}{}^{\gamma}$ value reported by Albanese and colleagues (1878 min) when sampling for 72 h after infusion.[29] However, no trend in $T_{1/2}{}^{\gamma}$ values was observed over a range of infusion sampling time (677–3090 min) by Bailie and colleagues.[30] In view of the difficulties of defining $T_{1/2}{}^{\gamma}$ with confidence and the difference between subjects in both groups in the number of exponential phases required to define the elimination kinetics, MRT values have also been compared between groups. There was no significant difference between groups for this parameter.

The propofol concentration associated with loss of consciousness was comparable with values reported in unpremedicated patients (2.09–4.4 μg ml^{-1})[31–33] and was therefore unexpectedly high in our group of premedicated patients. Recovery times in the ESRD patients were significantly shorter than those in the control patients. The amount of fentanyl given during the infusion was larger in the control group. This could have contributed to the difference in recovery times between groups. But this is unlikely as propofol concentrations at eyes open were similar in both groups and were in good agreement with published data (approximately 1 μg ml^{-1}).[19 26] Vuyk and colleagues demonstrated that return of consciousness is caused mainly by a reduction in the effect site propofol concentration and less by fentanyl decay.[35] Interestingly, Nathan and colleagues also noted a trend to a shorter emergence time in their uraemic group compared with control patients.[9]

There was no major haemodynamic instability justifying interruption of the infusion. This may have been because of the slow infusion rate used for induction. Peacock and colleagues demonstrated that in elderly patients, the slower the infusion rate the smaller were the decreases in arterial pressure.[34] Our infusion rate corresponded to a dose of 1.75 mg kg^{-1} over a 5-min period for induction of anaesthesia, which is lower than the standard induction dose used in clinical practice. Nevertheless, during anaesthesia, treatment with ephedrine to restore haemodynamic stability was more frequent in the ESRD group (total amount given 4 (8.4) mg) than in the control group (1.7 (3.5) mg) (ns). We believe that this was related to the volume status of these haemodialysed patients.

In summary, the pharmacokinetics of propofol infusion were similar in ESRD and control subjects. In particular, propofol clearance, which determines the steady state concentration during infusion, was unchanged in subjects with end-stage renal failure. This suggest that the kidney is not involved substantially in the extrahepatic metabolism of propofol. The manually controlled three-stage infusion to supplement nitrous oxide resulted in a satisfactory state of surgical anaesthesia in almost all patients, whether or not renal function was impaired. In both ESRD patients and patients with normal renal function, it is important that careful dose titration is used when administrating propofol by infusion.

References

1. Elston AC, Bayliss MK, Park GR. Effect of renal failure on drug metabolism by the liver. *British Journal of Anaesthesia* 1993; 71: 282–290.
2. Reidenberg MM. The biotransformation of drugs in renal failure. *American Journal of Medecine* 1977, **62**: 482–485.
3. Smith I, White P, Nathanson M, Gouldson R. PROPOFOL An update on its clinical use. *Anesthesiology* 1994; **81**. 1005–1043
4. Bryson HM, Fulton BR, Faulds D. PROPOFOL An update of its use in anaesthesia and conscious sedation *Drugs* 1995; **50**: 513–559
5 Gepts E, Trenchant A. Propofol. *Anaesthetic Pharmacology Review* 1995; **3**. 46–56.
6. Simons PJ, Cockshott ID, Glen JB, Gordon EA, Knott S, Ruane RJ Disposition and pharmacology of propofol glucuronide administered intravenously to animals. *Xenobiotica* 1992; **22**: 1267–1273.
7 Morcos WE, Payne JP. The induction of anaesthesia with propofol ('Diprivan') compared in normal and renal failure patients. *Postgraduate Medical Journal* 1985; **61** (Suppl 3)· 62–63
8. Kirvela M, Olkkola KT, Rosenberg PH, Yli-Hankala A, Salmela K, Lindgren L. Pharmacokinetics of propofol and haemodynamic changes during induction of anaesthesia in uraemic patients. *British Journal of Anaesthesia* 1992; **68**· 178–182.
9. Nathan N, Debord J, Narcisse F, Dupuis JL, Lagarde M, Benevent D, Lachatre G, Feiss P. Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and in renal failure patients: a preliminary study. *Acta Anaesthesiologica Belgica* 1993; **44**· 77–85
10. Plummer GF. Improved method for the determination of propofol in blood by high-performance liquid chromatography with fluorescence detection. *Journal of Chromatography* 1987; **421**· 171–176.
11 Colburn WA. Simultaneous pharmacokinetic and pharmacodynamic modeling *Journal of Pharmacokinetics and Biopharmaceutics* 1981; **9**: 367–388
12. Balant LP, Garrett ER. Computer use in pharmacokinetics. In: Garrett ER, Hirtz JL, eds. *Drug Fate and Metabolism, vol. 4.* New York· 1983
13. Loo JCK, Riegelman S Assessment of pharmacokinetic constants from post-infusion blood curves obtained after intravenous infusion. *Journal of Pharmacological Sciences* 1970, **59**: 53–55.
14 Machin D, Campbell MJ. *Statistical Tables for the Design of Clinical Trials. Medical Statistics and Computing* Oxford Blackwell Scientific Publications, 1987; **3**: 79–88.
15. Schwarz G. Estimating the dimension of a model *Annals of Statistics* 1978; **6**. 461–464.
16. Simons PJ, Cockshott ID, Douglas EJ, Gordon EA, Hopkins K, Rowland M. Disposition in male volunteers of a subanaesthetic intravenous dose of an oil in water emulsion of ^{14}C-propofol. *Xenobiotica* 1988; **18**: 429–440.
17. Cockshott ID, Douglas EJ, Prys-Roberts C, Turtle M, Coates DP. The pharmacokinetics of propofol during and after intravenous infusion in man. *European Journal of Anaesthesiology* 1990; 7: 265–275.
18. Gepts E, Jonckheer K, Maes V, Sonck W, Camu F. Disposition kinetics of propofol (Diprivan) during alfentanil anaesthesia *Anaesthesia* 1988; **43** (Suppl.). 8–13.
19. Shafer A, Doze VA, Shafer SL, White PF Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. *Anesthesiology* 1988, **69**: 348–356
20. Cockshott ID, Briggs LP, Douglas EJ, White M

Pharmacokinetics of propofol in female patients. *British Journal of Anaesthesia* 1987; **59**: 1103–1110.

21. Veroli P, O'Kelly B, Bertrand F, Trouvin JH, Farinotti R, Ecoffey C. Extrahepatic metabolism of propofol in man during the anhepatic phase of orthotopic liver transplantation. *British Journal of Anaesthesia* 1992; **68**: 183–186.
22. Mather LE, Selby DG, Runciman WB, McLean CF. Propofol: assay and regional mass balance in the sheep. *Xenobiotica* 1989; **19**: 1337–1347.
23. Verpoorte R. Potential effect of early blood sampling schedule on calculated pharmacokinetic parameters of drugs after intravenous administration. *Journal of Pharmaceutical Sciences* 1980; **69**,7: 867–869.
24. Coetzee JF, Glen JB, Wium CA, Boshoff L. Pharmacokinetic model selection for target controlled infusions of propofol. *Anesthesiology* 1995; **82**: 1328–1345.
25. Chiou WL. The phenomenon and rationale of marked dependence of drug concentration on blood sampling site: implications in pharmacokinetics, pharmacodynamics, toxicology and therapeutics. *Clinical Pharmacokinetics* 1989; **17**: 175–199.
26. Servin F, Cockshott ID, Farinotti R, Haberer JP, Winckler C, Desmonts JM. Pharmacokinetics of propofol infusions in patients with cirrhosis. *British Journal of Anaesthesia* 1990; **65**: 177–183.
27. Servin F, Farinotti R, Haberer JP, Desmonts JM. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. *Anesthesiology* 1993; **78**: 657–665.
28. Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS. Pharmacokinetics of propofol (Diprivan) in elderly patients. *British Journal of Anaesthesia* 1988; **60**: 146–150.
29. Albanese J, Martin C, Lacarelle B, Saux P, Durand A, Gouin F. Pharmacokinetics of long-term propofol infusion used for sedation in ICU patients. *Anesthesiology* 1990; **73**: 214–217.
30. Bailie GR, Cockshott ID, Douglas EJ, Bowles BJM. Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. *British Journal of Anaesthesia* 1992; **68**: 486–491.
31. Vuyk J, Engbers FHM, Lemmens HJM, Burm AGL, Vletter AA, Gladines MPR, Bovill JG. Pharmacodynamics of propofol in female patients. *Anesthesiology* 1992; **77**: 3–9.
32. Leslie K, Sessler DI, Smith WD, Larson MD, Ozaki M, Blanchard D, Crankshaw DP. Prediction of movement during propofol/nitrous oxide anesthesia. *Anesthesiology* 1996; **84**: 52–63.
33. Vuyk J, Martijn JM, Olofsen E, Burm AGL, Bovill JG. Propofol anesthesia and rationale opioid selection. *Anesthesiology* 1997; **87**: 1549–1562.
34. Peacock JE, Lewis RP, Reilly CS, Nimmo WS. Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients. *British Journal of Anaesthesia* 1990; **65**: 346–352.

British Journal of Anaesthesia 1998; **81**: 861–864

Changes in core temperature compartment size on induction of general anaesthesia

C. D. DEAKIN

Summary

A two-compartment model of temperature distribution estimates the core compartment to occupy 66% of body mass at rest, while the peripheral compartment comprises the remainder. General anaesthesia impairs thermoregulation by central and peripheral actions. Peripheral vasodilatation accelerates heat transfer from the core to peripheral compartment causing the core compartment to cool and expand in size. Core hypothermia may be a significant cause of postoperative morbidity. This undocumented change in the size of the core compartment on induction of anaesthesia can be calculated. Core size increased from the established value of 66% before induction of general anaesthesia to 71.2 (SD 6)% of body mass, 20 min after induction of anaesthesia (P=0.0001). On induction of general anaesthesia, the core compartment cools and expands while the peripheral compartment warms and contracts by a corresponding amount. Measurement of the magnitude of changes in core:periphery heat distribution on induction of anaesthesia contribute to a clearer understanding of the pathophysiology of perioperative hypothermia. (*Br. J. Anaesth.* 1998; **81**: 861–864).

Keywords: temperature, core; temperature, periphery; anaesthesia, general

Normal physiological function requires intact thermoregulatory mechanisms. General anaesthesia impairs thermoregulation by central and peripheral actions. The resultant perioperative hypothermia occurs in three distinct stages.[1] This study examines the initial stage in which peripheral vasodilatation accelerates heat transfer from the core to peripheral compartment. This heat redistribution causes the core compartment to cool and expand with minimal change in overall total body heat content. This unquantified expansion of core size may contribute to the second stage of anaesthesia-induced hypothermia as the core compartment expands towards the body surface and accelerates heat loss. The resulting mild to moderate hypothermia is likely to increase perioperative morbidity by causing increased myocardial workload, impaired oxygen delivery and impaired coagulation. Calculation of both the magnitude and rate of change in core size may further elucidate the pathophysiology of perioperative hypothermia and enable the development of techniques to improve the efficiency of active postoperative rewarming. Core size after induction of anaesthesia was therefore measured to determine the magnitude and rate of these changes.

Patients and methods

The study was approved by Southampton Joint Ethics Committee, and all patients gave written informed consent. Six adult elective surgical patients were studied before and after induction of general anaesthesia. The general anaesthetic technique and patient characteristics were matched as closely as possible to the technique used during the calculation of total heat content after induction of general anaesthesia.[2] No premedication was given. Anaesthesia was induced with propofol 3 mg kg^{-1} i.v., fentanyl 2–3 μg kg^{-1} i.v. and vecuronium 0.1 mg kg^{-1} i.v. The trachea was intubated and the lungs ventilated with a Penlon 200 ventilator using oxygen:nitrous oxide (FI_{O_2}>=0.40) to maintain normocapnia (Pa_{CO_2} 3.5–4.5 kPa). A heat and moisture exchanging filter (Mallinckrodt Medical Hygrobac "S") was placed on the catheter mount. Anaesthesia was maintained using 0.5–0.75% end-tidal isoflurane. Patients were covered with a light wool blanket before induction of anaesthesia and during temperature recordings. Room temperature was maintained at 22°C.

Core temperature (Tc) was measured with a tympanic membrane thermocouple probe (Mallinckrodt, Northampton, UK) placed before induction of anaesthesia after confirmation that the external auditory meatus was free from wax. Mean peripheral temperature (Tp) was recorded with four calibrated thermistors (Yellow Springs 400) placed on the upper arm, lateral chest wall, lateral thigh and lateral calf (Tp=0.3 (chest wall+upper arm)+0.2 (leg + thigh)).[3] Temperature data were recorded to a temperature logger[4] at 1-min intervals for 5 min before and 20 min after induction of general anaesthesia.

CALCULATION OF CORE COMPARTMENT SIZE

Calculation of core compartment size makes several assumptions which are considered in detail in the discussion: (1) a two-compartment (core and periphery) model of heat distribution; (2) core mass under thermoneutral conditions represents 66% total body mass[5]; (3) specific heat capacity is identical for core

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and peripheral compartments[6]; and (4) after induction of general anaesthesia, net body heat content decreases at 0.026 kJ^{-1} kg^{-1} min^{-1}.[2]

The derivation of the core compartment size is detailed in the appendix.

STATISTICAL ANALYSIS

Results are given as mean (SD). Changes in core and peripheral temperature were analysed by analysis of variance (ANOVA). Significance was taken as $P<0.05$.

Results

The mean age of the patients was 53.7 (range 32–74) yr, mean weight was 65.2 (SD 8.9) kg and mean body mass index was 22.1. The anaesthetic room temperature was maintained at 22.1±0.3°C with humidity of 39.7±3.2%.

After induction of anaesthesia, core temperature decreased by 0.63 (0.32)°C from 37.0 (0.27)°C to 36.4 (0.45)°C over a 20-min period ($P=0.0001$). Over the same period, mean peripheral temperature increased by 0.32 (0.22)°C from 33.0 (0.74)°C to 33.28 (0.70)°C ($P<0.01$) (fig. 1). Core size increased from the established value of 66% before induction of general anaesthesia to 71.2 (6)% of body mass, 20 min after induction of anaesthesia ($P<0.01$) (fig. 2).

Discussion

These results show that over a 20-min period after induction of general anaesthesia, core temperature compartment size increased from 66% to 71% of total body mass, while the peripheral compartment decreased from 34% to 29%. After induction of general anaesthesia, the core compartment cools and expands while the peripheral compartment warms and contracts. This is the first study to document the magnitude of these changes.

Under normal physiological conditions, thermal energy is transferred from the core to the periphery down a temperature gradient. Most thermal energy is transferred by blood flow from core to peripheral tissues. Anaesthetic-induced inhibition of thermoregulatory vasoconstriction increases peripheral blood flow and accelerates heat transfer from the core to the periphery.[1] The subsequent decrease in core temperature and increase in peripheral temperature is well documented.[2 7 8] Redistribution of heat accounts for 87% of the decrease in core temperature that occurs over the initial 30 min after induction of general anaesthesia, the remainder being caused by the 20% reduction in metabolic heat production and increased heat loss.[9]

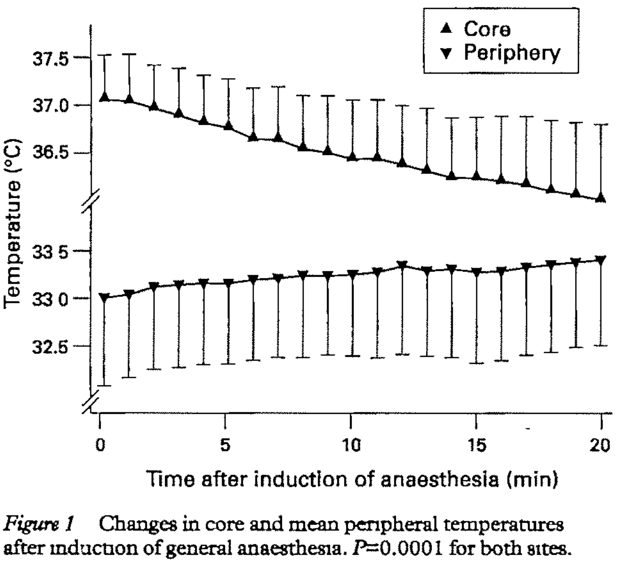

Figure 1 Changes in core and mean peripheral temperatures after induction of general anaesthesia. $P=0.0001$ for both sites. Error bars represent 1 SD.

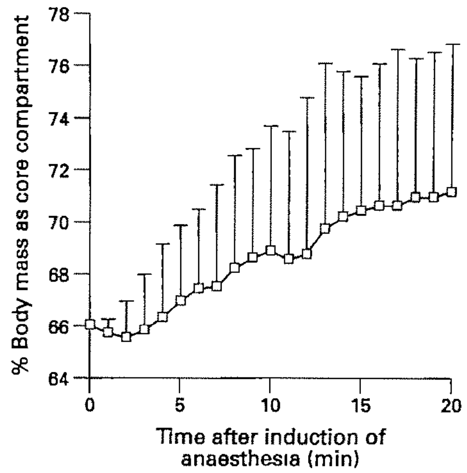

Figure 2 Changes in percentage core size after induction of general anaesthesia. $P=0.0001$. Error bars represent 1 SD

Changes in core and peripheral size occur only in approximately the first 30 min after induction of general anaesthesia after which time heat loss exceeds heat production and both core and peripheral compartments cool further.[1] As the peripheral compartment cools, thermoregulatory vasoconstriction decreases peripheral heat loss and acts to sequester heat within the core compartment.[1] Under these conditions it has been proposed that the core compartment retracts to a size smaller than normal (i.e. less than 66% of total body mass)[1] but no calculations have been made to support this theory. Changes in core size have previously been calculated only in hot environments (45°C) where total body heat content increases and core size expands to 79% of total body mass.[5]

The results of this study were calculated based on several assumptions. One anatomical site is used to represent mean core temperature. It is a method used regularly in thermoregulatory studies. Tympanic membrane temperature correlates well with cerebral, oesophageal, nasopharyngeal and pulmonary artery catheter temperature and is regarded as the "gold standard" for core temperature measurements by many authors.[10] Variation in temperature between these sites is less than 0.5°C under normothermic conditions. Changes in core temperature are rapidly detected at the tympanic membrane and is therefore considered an appropriate site to represent core temperature in this study.

Peripheral temperature is more variable between sites because it is the site of thermoregulatory vasoconstriction. Within the tissue itself, small temperature variations occur between septa dividing fatty layers and different tissues[11] but temperature of tissues regarded as "peripheral" usually varies by no more than 5°C except in the presence of moderate to severe hypothermia where peripheral vasoconstriction of fingers and toes can be severe. Skin covering the limbs is the coldest of peripheral sites under most conditions, whereas that covering the trunk is warmer.[12] A weighted average is used to calculate a mean value and has been shown to be a reasonable approximation to the true value.[13]

Two-compartment modelling of temperature distribution is a concept established in early studies of thermoregulation[11,14,15] and is used widely for modelling perioperative thermal changes. The transition from core to peripheral compartment occurs at varying depths at different anatomical sites. Core temperature extends to within 2.5–7 mm from the skin over tissues of the upper arm and thigh.[11,15] In more peripheral tissue, core temperature may not extend so close to the surface. A recent study established that while tissues 18 mm deep to the sole of the foot correlated well with core temperature (r^2=0.87), a poorer correlation was shown with tissue at 8 mm depth (r^2=0.75).[16] Rectal and vaginal temperature have been documented as not reaching maximum values until a depth of 5 cm in each cavity was reached.[15] However, rectal temperature is recognized as being slightly higher than true core temperature through the effects of thermogenic bacteria and thus this depth may be only an approximation. Thus core temperature appears to extend to within a few centimetres of all body surfaces where it decreases by approximately 5°C across the peripheral compartment. The apparent extension of the core compartment to within a few centimetres of the body surface and the sharp decrease in temperature close to the body surface allows approximation to a two-compartment model. The two-compartment model allows calculation of core and peripheral heat distribution at rest,[5] after induction of general anaesthesia[2] and during hyperthermia.[5] It has also been used to investigate the effect of morphometric characteristics on perioperative hypothermia[7,17] and is central to an understanding of the mechanisms causing postoperative hypothermia in patients after hypothermic cardiopulmonary bypass.[18,19]

Calculation of energy content of tissues assumes that tissues of core and peripheral compartments have similar specific heat capacity (SHC). SHC of tissue (heart, liver, kidney, brain, spleen, blood) contained within the core compartment varies from 3.60 to 3.89 kJ kg^{-1} K^{-1}. Although there are no specific studies, bone can be regarded as mostly at core temperature but has a significantly lower SHC of 1.30 kJ kg^{-1} K^{-1}. Tissues of the peripheral compartment are mostly skin, subcutaneous fat and some muscle. SHC of skin is 3.47 kJ kg^{-1} K^{-1}, fat 2.30 kJ kg^{-1} K^{-1} and muscle 3.72 kJ kg^{-1} K^{-1}.[6,20,21] Difficulties exist in determining the amount of tissues such as fat, bone and muscle that should be allocated to each compartment. In addition, changes in core size with hypothermia change the proportions of tissue within each compartment. Thus determination of mean SHC of core and peripheral compartments involves several unknown variables. No estimates have been made of mean values for core and peripheral compartments but it is thought that use of a mean value for both compartments is an adequate approximation for the calculation of thermal energy content.[22]

The change in body heat content after induction of general anaesthesia is small. In six separate studies, estimates of net heat loss during anaesthesia have varied between 42 and 130 kJ h^{-1}.[9,13] This variability appears to be caused by different anaesthetic techniques and differences in room temperature at which the studies were carried out. Different anaesthetic techniques may vary both in their effects on the internal redistribution of body heat and the ensuing rate of heat loss. The results of this study are specific both to the anaesthetic technique and room temperature, but because changes in heat content as a proportion of total body heat are small, it is likely that core size will change by similar magnitude when using other anaesthetic agents.

Heat loss on induction of anaesthesia calculated by Matsukawa and colleagues used the most accurate methodology of any study.[2] Six minimally clothed volunteers were anaesthetized and studied for 3 h at a room temperature of 22°C during which overall heat balance was determined from the difference between cutaneous heat loss (thermal flux transducers) and metabolic heat production (oxygen consumption). Arm and leg tissue heat content was determined by the use of 19 i.m. thermocouples, 10 skin temperatures and "deep" foot temperature. Data from this work were therefore used for this study to calculate total body heat at any given time after induction of general anaesthesia. Caution must be exercised when applying data from one study to another, but anaesthetic technique and environmental conditions were matched closely in the study population and the subsequent changes in core and peripheral temperatures were of similar magnitude in both studies. There was a difference in body mass index (BMI) which was higher in the study by Matsukawa and colleagues (25.6 *vs* 22.1). Although body fat has been regarded as an insulating layer, the effect of body fat on heat loss is variable and some studies have shown no effect on heat loss during anaesthesia.[7] Increased body fat content reduces the amount of redistribution hypothermia during the first hour of anaesthesia but the effects are most marked at extremes of body fat content.[17] The small differences in BMI and subsequent differences in heat loss between the two groups is small and the effects on calculation of core size are therefore minimal.

This study was limited to a 20-min period after which patients were moved to the operating theatre and surgery began. At this stage, many variables make further calculations of body heat content inaccurate through immeasurable heat loss from removal of insulating blankets,[23] application of cold surgical cleaning fluid, cooling by convection from theatre ventilation, evaporative water loss from open body cavities and loss of heat in body fluids.[1] The rate of heat loss documented by Matsukawa and colleagues[2] and used for these core size calculations was measured in subjects in a stable environment and therefore cannot be applied when the patient is moved to the operating theatre where heat loss during surgery is approximately twice that documented in the stable environment of the anaesthetic room.[23]

Initial redistribution hypothermia is followed by a distinct second stage in which heat loss exceeds metabolic heat production to cause a slow decrease in core temperature. The increased heat loss during this second stage may be contributed to by the expansion of core compartment towards the body surface resulting in a greater rate of heat loss across the shallower peripheral compartment. This study has documented for the first time changes in heat distribution in the first of three stages of anaesthetic-induced hypothermia. It is hoped that the results will be a useful measure in the study of the pathophysiology of hypothermia under anaesthesia.

Appendix

Total body heat content in a resting state, before induction of general anaesthesia can be calculated from the equations:

Mean body temperature (Tb)[5]

$$Tb = 0.66\,Tc + 0.34\,Tp \qquad (1)$$

Total body heat content (Qb)[5]

$$Qb = Mb.\,s.\,Tb \qquad (2)$$

where s=mean specific heat capacity of human tissue (3.475 kJ kg^{-1} K^{-1}); Qb=total body heat content; Qc=total core heat content; Qp=total peripheral heat content; Tb=mean body temperature; Tc=mean core (tympanic membrane) temperature; Tp=mean peripheral temperature; Mb=total patient mass, Mc=core mass; and Mp=peripheral mass.

After induction of general anaesthesia, total body heat content decreases linearly at 0.026 kJ^{-1} kg^{-1} min^{-1} (130 kJ h^{-1}).[2] Using the same anaesthetic technique, total body heat content at time "t" after induction of anaesthesia can be calculated from the equation:

$$Qb_t\,(kJ) = Qb_0 - (0.026.\,Mb.\,t)$$

where Qb_0=total body heat content before induction of anaesthesia; and Qb_t=total body heat content at time "t".

Calculation of core (x) compartment size at time "t" can be made by re-arranging the equation.

$$Qb_t = (s.\,Tc_t.\,Mb.\,x) + (s.\,Tp_t.\,Mb.\,(1-x))$$

where x=core size; Tc_t=mean core temperature at time "t"; Tp_t=mean peripheral temperature at time "t"

Calculations for the derivation of "x" are outlined below.

$$Qb = Qc + Qp \qquad (3)$$

$$Qb = (Tc.\,s.\,Mc) + (Tp.\,s.\,Mp) \qquad (4)$$

But $Mp=Mb-Mc$ and therefore, combining equations (2) and (4):

$$Qb = (Tc.\,s.\,Mc) + (Tp\ s\ Mb) - (Tp.\,s.\,Mc) \qquad (5)$$

Rearranging equation (5):

$$Qb - (Tp.\,s.\,Mb) = (Mc.\,s)(Tc - Tp) \qquad (6)$$

$$Mc = \frac{Qb - (Tp.\,s.\,Mb)}{s.\,(Tc - Tp)} \qquad (7)$$

After induction of general anaesthesia, body heat content decreases at 0.026 kJ^{-1} kg^{-1} min^{-1}. Thus at a time "t":

$$Qb_t = Qb_0 - (0.026.\,Mb\ t) \qquad (8)$$

Therefore, from equation (7):

$$Mc_t = \frac{Qb_0 - (0.026\,Mb.\,t) - (Tp_t\ s.\,Mt)}{s\,(Tc_t - Tp_t)} \qquad (9)$$

$Qb_0 = Mb.\,s.\,Tb_0$ from equation (2)

Substitute

$$Mc_t = \frac{(Mb.\,s.\,Tb_0) - (0.026\,Mb.t) - (Tp_t.\,s.\,Mb)}{s\,(Tc_t - Tp_t)} \qquad (10)$$

$$Mc_t = \frac{Mb\,(s\,(Tb_0 - Tp_t) - 0.026\,t)}{s\,(Tc_t - Tp_t)} \qquad (11)$$

$$\frac{Mc_t}{Mb} = \frac{s\,(Tb_0 - Tp_t) - 0.026\,t}{Tc_t - Tp_t} \qquad (12)$$

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References

1. Sessler DI. Perianesthetic thermoregulation and heat balance in humans. *FASEB Journal* 1993; 7. 638–644.
2. Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C. Heat flow and distribution during induction of general anaesthesia. *Anesthesiology* 1995; **82**: 662–673.
3. Ramanathan NL. A new weighting system for mean surface temperature of the human body. *Journal of Applied Physiology* 1964; **19**: 531–533.
4. Petley GW, Clitheroe S, Clewlow F, Deakin CD, Chauhan AJ. Development and application of a general purpose ambulatory monitor. *Medical Engineering and Physics* 1998; **20**: 33–39.
5. Colin J, Timbal J, Houdas Y, Boutelier C, Guieu JD. Computation of mean body temperature from rectal and skin temperature. *Journal of Applied Physiology* 1971; **31**: 484–489.
6. Cooper TE, Trezek GJ. Correlation of thermal properties of some human tissue with water content. *Aerospace Medicine* 1971; 42: 24–27.
7. Holdcroft A, Hall GM. Heat loss during anaesthesia. *British Journal of Anaesthesia* 1978; 50: 157–164.
8. Shanks CA. Mean skin temperature during anaesthesia: an assessment of formulae in the supine surgical patient. *British Journal of Anaesthesia* 1975; 47: 871–875.
9. Sakuragi T, Mukai M, Dan K. Deep body temperature during the warming phase of cardiopulmonary bypass *British Journal of Anaesthesia* 1993; 71: 583–585.
10. Bazett HC, McGlone B. Temperature gradients in the tissues in man. *American Journal of Physiology* 1927; **82**: 415–451.
11. Sessler DI: Temperature monitoring. In: Miller RD, ed. *Anesthesia*, 3rd Edn. New York: Churchill Livingstone, 1995; 1227–1242.
12 Imrie MM, Hall GM. Body temperature and anaesthesia. *British Journal of Anaesthesia* 1990; **64**. 346–354.
13. Burton AC. Human calorimetry: average temperature of tissues of the human body. *Journal of Nutrition* 1935; **9**: 261–280.
14. Benedict FG, Slack EP. A comparative study of temperature fluctuations in different parts of the human body. *Carnegie Institute of Washington* 1911; **155**: 1–73.
15. Matsukawa T, Kashimoto S, Ozaki M, Shindo S, Kumazawa T. Temperatures measured by a deep body thermometer (Coretemp) compared with tissue temperatures measured at various depths using needles placed into the sole of the foot. *European Journal of Anaesthesiology* 1996; **13**. 340–345.
16. Kurz A, Sessler DI, Narzt E, Lenhardt R, Lackner F. Morphometric influences on intraoperative core temperature changes. *Anesthesia and Analgesia* 1995; **80**: 562–567.
17. Duthie DJ, Woolman PS, Doyle AR. Enoximone and warming after hypothermic cardiopulmonary bypass. *British Journal of Anaesthesia* 1995; 75: 43–46.
18. Noback CR, Tinker JH. Hypothermia after cardiopulmonary bypass in man: amelioration by sodium nitroprusside induced vasodilation during rewarming. *Anesthesiology* 1980; **53**: 277–280.
19. Diem K, Lentner C. *Documenta Geigy. Scientific Tables*, 7th Edn. Macclesfield: Geigy Pharmaceuticals, 1970; 560.
20. Duck FA. *Physical Properties of Tissue. A Comprehensive Reference Book*. London. Academic Press Ltd, 1990.
21. Plattner O, Xiong J, Sessler DI, Schmeid H, Christensen R, Turakhia M, Dechert M. Rapid core-to-peripheral tissue heat transfer during cutaneous cooling. *Anesthesia and Analgesia* 1996; **82**: 925–930.
22. Sessler DI, McGuire J, Sessler AM. Perioperative thermal insulation. *Anesthesiology* 1991; 74: 875–879.
23. Stjernström H, Henneberg S, Eklund A, Tabow F, Arturson G, Wiklund L. Thermal balance during transurethral resection of the prostate. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 743–749.

British Journal of Anaesthesia 1998; **81**: 865–869

Intranasal midazolam for premedication of children undergoing day-case anaesthesia: comparison of two delivery systems with assessment of intra-observer variability

N. GRIFFITH, S. HOWELL AND D. G. MASON

Summary

Midazolam is often used for paediatric premedication. We have compared two methods of administering midazolam intranasally in 44 surgical day-case children allocated randomly to receive midazolam 0.2 mg kg^{-1} as drops or midazolam 0.1 mg kg^{-1} from an intranasal spray device. Behaviour was recorded on a four-point scale by the parent, nurse and anaesthetist. Coefficients were obtained representing the change in behaviour score. There was no significant difference in method of administration (coefficient 0.13, P=0.39). Children were significantly more distressed at the time of premedication and at the time of venous cannulation (coefficients 1.31 and 0.70) than at baseline. There was no significant difference in the assessments between observers. Midazolam by either method was equally effective but acceptability of the premedication was poor in both groups. Intranasal midazolam cannot be recommended as a method for routine premedication of young children. (*Br. J. Anaesth.* 1998; **81**: 865–869).

Keywords: hypnotics benzodiazepine, midazolam; premedication, midazolam; anaesthesia, paediatric; anaesthesia, day case

In paediatric day-case anaesthesia, premedication may be required to minimize psychological stress or to control a distressed child. If used, it needs to be in an acceptable form, to have a rapid onset with minimal hangover effect and to have few side effects. Amnesia for transfer and entry to the operating theatre and a smooth induction may also be desired to reduce anxiety at subsequent visits.

Midazolam, a water soluble, short-acting 1, 4-benzodiazepine, may be administered by various routes. Oral and rectal routes are used widely and provide effective sedation. However, some authorities have expressed concern about the wide bioavailability when given by these routes, ranging from 18% to 44% with an appreciable first-pass effect.[1-5] I.m. administration is painful and the sublingual route is effective but has poor compliance.[6] The intranasal route for midazolam has been used since 1988 and has the advantage of rapid absorption directly into the systemic circulation with no first-pass effect and a bioavailability of 55–83%.[7-10] However, the delivery method appears to be poorly tolerated and threatening, with poor retention of drops and drainage into the post-nasal space.[11]

Midazolam 0.1–0.2 mg kg^{-1} by nasal drops from a syringe provides adequate plasma concentrations and good effect within 10–12 min.[12 13] As a fine spray, the drug can be delivered well into the nasal cavity, avoiding spillage and swallowing seen with drops and thus allowing a smaller dose to be used.[10] Our primary aim was to determine if application by spray delivery was practicable and if it would be less unpleasant while still being as effective as drops.

Assessing distress in children is subjective. We also compared assessments of each subject's distress made by three different observers: the child's parent, a ward nurse and the study anaesthetist (N. G.) using a numerical rating score modified from Davis and colleagues.[14]

Patients and methods

After obtaining approval from the Institutional Ethics Committee and informed written consent from parents, we studied 44 children, weighing less than 30 kg, aged 1–8 yr. All patients were ASA I or II and were undergoing elective day surgery in the paediatric day unit. Patients were excluded if there was parental or child refusal or if there were nasal secretions.

The children were allocated randomly by the toss of a coin to receive commercially available i.v. midazolam (5 mg ml^{-1}, Hypnovel, Roche) intranasally by one of two applicators. Group D received midazolam 0.2 mg kg^{-1} as drops from a 1-ml syringe (n=20) and group S received midazolam 0.1 mg kg^{-1} as a spray from a nasal pump (n=24), in each case corrected to the nearest 0.5 mg. A lower dose was given using the spray, as better delivery and absorption were expected with this route of administration, as shown by better bioavailability.[10]

EMLA cream was applied to the dorsum of both hands. Resuscitation equipment was available, including flumazenil 0.5 mg ml^{-1}. Premedication was administered in the treatment room on the ward by the study anaesthetist (N. G.) just before the patient went to theatre. The child sat facing forwards on the parent's lap while their arms were gently restrained by one parental hand and the other hand used to tilt the forehead back 15°. Premedication was given by

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the study anaesthetist to one nostril using either a 1-ml syringe or a nasal pump spray (Perfect-Valois UK Ltd, Pump VP3/140 18ph White Plastic Gasket No 400, Diptube 32mm) and modified bottle into which conveniently fitted a 2-ml midazolam 5 mg ml^{-1} ampoule (fig. 1). The metered dose with each spray had a volume of 0.1 ml equivalent to midazolam 0.5 mg.

Each child's behaviour was scored on a four-point scale presented on a printed card as follows: 1=unafraid, calm, playing and relaxed; 2=calm with reassurance, suspicious; 3=miserable, afraid, anxious; 4=crying, clinging, combative. Scores were obtained separately and independently from three observers: parent, ward nurse responsible for the child and N. G., at the following times: before premedication (baseline), immediately after premedication, on arrival in theatre and at cannulation.

The parent and N. G. were both present throughout the study. They gave their scores for the effect of the premedication immediately after administration of midazolam. The nurse left the room before administration of midazolam and returned to give her score approximately 3 min later. Thus the nurse was blind to the mode of premedication and her score was given slightly later than that of the parent and N. G. She then accompanied the child to theatre with the parent and N. G. Four different nurses were present on the ward during the study, but the same nurse followed through each child.

On arrival in the anaesthetic room, vein cannulation was performed using a 22-gauge Venflon and i.v. induction was performed in preference to inhalation induction. Analgesia was provided with rectal diclofenac 1 mg kg^{-1} and local blocks where appropriate. Any complications were noted.

Behaviour at induction was assessed by the anaesthetist, and that at recovery by the recovery nurse, as either good or poor. Both were unaware of whether or not the child had received premedication. The child was sent to the ward when fully awake. Before discharge home, the parents and child (if old enough) were asked to comment on the acceptability and effectiveness of the route of premedication.

Data were analysed using STATA 5.0 from Windows '95 running on a Dell Latitude XPi CD. Descriptive statistics were produced for the two patient groups. Median (range) values were reported for continuous variables and proportions for categorical variables. The groups were compared using unpaired t tests for continuous variables and Fisher's exact test for categorical variables.

The effects of type of delivery system, observer and time of observation were examined by multiple linear regression modelling. Indicator variables were used to identify treatment with drops, two of the observers (the nurse and anaesthetist), and time periods after baseline. This gave a regression model which described the behaviour score for a child in terms of a baseline value plus coefficients, indicating the delivery system, time period and observer:

$$\text{Behaviour score} = \text{baseline} + \text{observer}_1(x) + \text{observer}_2(x) + \ldots \text{etc.}$$

As the nurse made her observation approximately 3 min after the parent and anaesthetist, an interaction term was introduced to examine specific differences between the other observers at this time. Coefficients were examined using a t test. $P<0.05$ was taken as significant and robust standard errors were used as repeated measures were being taken on the same patient at different times.

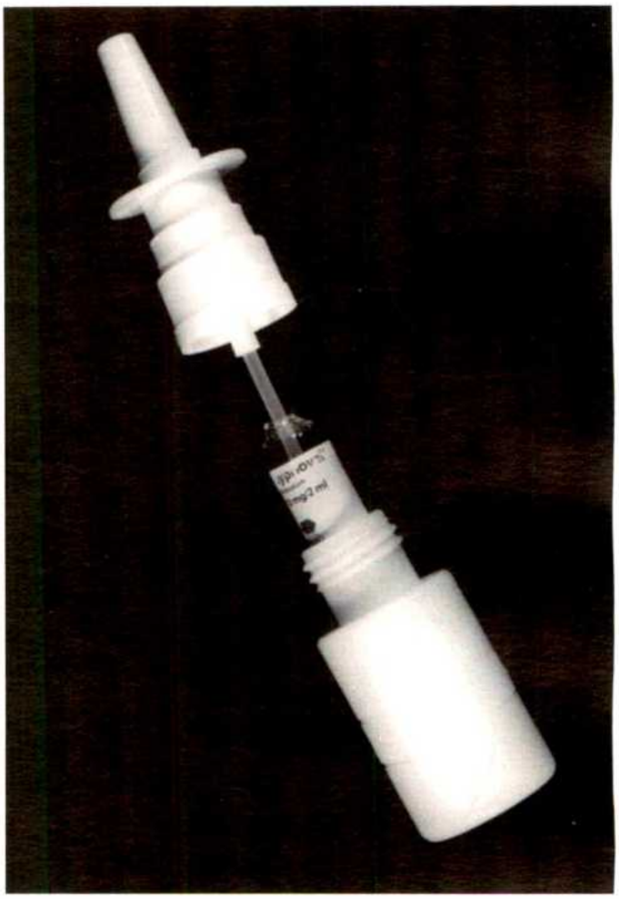

Figure 1 Intranasal spray device.

The use of robust standard errors allows the assumption of the independence of observations to be relaxed. Conceptually they may be viewed as being estimated by repeated sampling of the dataset with replacement (as in the bootstrap method). In STATA they are calculated by Huber's method (also known as the sandwich estimator of variance) which allows robust standard errors to be calculated without having to fit the model a large number of times.[15]

Results

We recruited 44 children: 20 children in the drops group (group D) and 24 in the spray group (group S). Only one child who had been randomized (group D) refused the premedication. Five others did not receive the complete dose: one in group D where the drops were seen to drip out of the nares and four in group S who moved before all the metered spray doses had been administered. All patients were included in the statistical analysis as the data were analysed on the basis of intention to treat.

Both groups were similar in age, weight, previous operations, type of anaesthesia and surgery, and induction and recovery behaviour (table 1). No child stayed in hospital overnight. The behaviour scores for the two study groups, as given by the three observers, are reported in table 2.

Table 1 Patient characteristics (median (range) or number)

	Group D (midazolam drops 0.2 mg kg^{-1}) (n=20)	Group S (midazolam spray 0.1 mg kg^{-1}) (n=24)
Age (yr)	4.5 (1.3–8.2)	4.8 (1–8.5)
Weight (kg)	17.3 (10.4–25.5)	17.9 (10–27.8)
Previous operation	4	5
Method of induction		
I.v.	19	21
Inhalation	1	3
Procedure		
Circumcision	6	7
Hernia repair/hydrocele	3	3
Orchidopexy/PPV	6	6
Umbilical hernia repair	1	2
Other	4	6
Behaviour at induction		
Good	19	19
Poor	1	5
Behaviour in recovery		
Good	17	20
Poor	3	4

A linear regression model was generated to describe the data (table 3). The coefficients and confidence intervals (CI) in the equation were as follows: the constant in the equation indicating the behaviour score of a child in group S, at baseline, as observed by the parent, was 1.44 (95% CI 1.15–1.72); the coefficient for the effect of drops compared with the spray was 0.13 (95% CI –0.29–0.56). There was no significant difference in scores between the two methods of administering midazolam (*t*=1.00, 1 df, *P*=0.39).

The coefficients for premedication, arrival in theatre and cannulation were positive, indicating that the children were significantly more distressed at these times than at baseline. At the time of premedication, coefficients were 1.31 (95% CI 1.22–1.41, *t*=43.49, 1 df, *P*>0.0001), at the time of arrival in theatre, 0.09 (95% CI 0.09–0.10, *t*=95.09, 1 df, *P*>0.0001) and at the time of cannulation, 0.70 (95% CI 0.69–0.70, *t*=322.39, 1 df, *P*>0.0001). The coefficient for time of premedication was greatest, reflecting the fact that children were most distressed at this time. While statistically significant, the coefficient of 0.09 for arrival in theatre was not clinically significant.

There were no significant differences between the scores given by the three observers. For the nurse, coefficients were –0.17 (95% CI –0.52–0.18, *t*=–1.50, 2 df, *P*>0.23) and for the study anaesthetist, –0.21 (95% CI –0.5–0.08, *t*=–2.3, 2 df, *P*>0.11).

The nurse observing the child after premedication found the child to be less upset than the other observers. The interaction term was negative and highly significant (–0.79, 95% CI –0.08 to –0.49, *t*=–8.58, 1 df, *P*>0.0001). The residuals from the linear regression model were normally distributed and their values were independent of the predicted values, indicating that this was an adequate model for the data.

Behaviour at induction was recorded as good by the case anaesthetist for 19 of 20 children in group D and for 19 of 24 children in group S. Similarly, behaviour on awakening was recorded by the recovery nurse as good for 17 of 20 children and for 20 of 24 children in groups D and S, respectively (table 1).

The majority of children found premedication administered by the nasal route unpleasant, whether given by spray or drops. Most complained of unpleasant taste and younger children dribbled. A smaller proportion complained of stinging in the nose, with younger children rubbing their noses—this was more common in group S (13 of 24 children compared with seven of 20 in group D). Half of the children in each group cried and only one of the 43 children neither cried nor complained.

On later questioning, 14 of 20 children in group D were old enough to comment and described the premedication as "horrible". One had refused the premedication and five others were too young to comment but had cried and been upset. Of the 16 patients old enough to comment in group S, 15 described the premedication as "horrible" and one as "okay". The other eight children were too young and had cried on administration. Only one child in group S, aged 4.5 yr, neither complained of the taste nor stinging, did not cry and described the premedication as okay.

Table 2 Behaviour scores at specified times from the parent, nurse and anaesthetist (mean (SD))

	Baseline score		Premedication score		Theatre arrival score		Cannulation score	
	Drops	Spray	Drops	Spray	Drops	Spray	Drops	Spray
Parent	1.6 (0)	1.4 (0 6)	3.3 (0.9)	2.7 (0.8)	1.6 (0.6)	1.3 (0.6)	2.1 (1.0)	2.3 (0.9)
Nurse	1.5 (0.5)	1.2 (0.5)	2.0 (0.9)	1.7 (0.8)	1.7 (0.6)	1.4 (0.6)	1.8 (0.9)	2.1 (1.1)
Anaesthetist (N. G.)	1.5 (0.6)	1.4 (0.5)	2.6 (1.1)	2.4 (0.9)	1.5 (0.7)	1.3 (0.6	1.8 (0.8)	2 3 (1.0)

Table 3 Linear regressions describing data

	Coefficient	Robust standard error	*t*	*P*	95% confidence interval
Drops	0.13	0.13	1.00	0.39	–0.29–0 56
Time of premedication	1.31	0.03	43.49	<0.001	1.22–1.41
Time of arrival in theatre	0.09	0 0009	95.09	<0.001	0.09–0 10
Time of cannulation	0.70	0.002	322.39	<0.001	0.69–0.70
Observer—nurse	–0.17	0.11	–1 50	0 23	–0.52–0.18
Observer—anaesthetist	–0.21	0.09	–2.30	0 11	–0.50–0.08
Interaction term=nurse observer for premedication	–0.79	0.09	–8.58	0.003	–1.08 to–0.49
Constant	1.44	0.09	15.80	0.001	1.15–1.72

No child became excessively sleepy and there were no complications related to administration, although one child in group S had a minor nose bleed the following day.

Discussion

Minor surgery and day-case anaesthesia can cause great distress for both children and their parents. Previous surgery with possible frightening memories has been identified as a factor causing postoperative anxiety reactions; amnesia of these events is desirable in paediatric patients.[16–18]

Numerous authors have searched for the ideal paediatric premedicating agent and also for the best route of administration.[6 7 11 18–24] A premedicant must have an acceptable, atraumatic route of administration in addition to other characteristics needed for such a drug. Intranasal midazolam solution is not marketed, but the commercially available 5-mg ml^{-1} i.v. solution can be used. Most studies have used midazolam 0.1–0.2 mg kg^{-1} and several pharmacokinetic studies have examined plasma concentrations and effect at varying intranasal doses.[7–13 20 23 25–28]

Intranasal midazolam has generally been administered in the form of drops, which in the awake patient are difficult to keep in the nose and may be swallowed and subjected to first pass metabolism in the liver. Some studies have indicated the actual mode and device of application but few give an idea of acceptance. Twersky and colleagues used a Devilbiss 286 atomizer to deliver 0.2 mg kg^{-1} but did not mention acceptability.[17] Bjorkman, Rigemar and Idvall used a spray bottle in adults and commented that some patients found the solution slightly irritating but all found the procedure acceptable.[10] Other authors have mentioned temporary distress, burning, unpleasant taste, sneezing, stinging, coughing, swallowing or crying.[6 7 11–13 20 25] Many do not discuss adverse reactions to application; omission may signify unpleasantness.[15] Midazolam has been given to adults by nebulizer with good acceptability.[29]

Assessing distress in children may be difficult. We compared assessments of behaviour made by the parent, doctor and nurse, and found no significant differences. There was also no significant difference between nasal drops and spray with regard to distress experienced by children. They were noted to be significantly upset at the time of premedication as judged by both the parent and study anaesthetist. The nurse, who observed the child approximately 3 min after premedication, did not observe the same degree of distress, suggesting that the distress is short-lived. However, on later questioning, 97% of children able to comment had been frightened by the mode of premedication and described it as "horrible". This recall of an unpleasant response could make the child more fearful of another visit to hospital.

It had been surmised that the fine aerosol would allow greater contact with the absorbing surface and that application would be less unpleasant than drops. Bioavailability with spray has been shown to be high (83%) with virtually complete absorption[10]; however, this greater contact seems to cause more nasal stinging than drops. One Indian child described the spray as like having hot red chillies up his nose. The stinging may be caused by the acidity of midazolam (pH 3.5) sensitizing pain receptors in the distribution of the trigeminal nerve in the nasal mucosa, affecting a greater area with the spray than with the drops. The spray and drops caused an equal incidence of unpleasant taste implying that even as an aerosol the solution did not remain within the nasal cavity and reached the taste receptors in the oropharynx and on the posterior tongue via the post-nasal space. It is surprising that the drops did not cause a greater taste sensation than the spray, as more seemed to reach the mouth.

Administration as a spray is complicated by the need to keep the head still for multiple applications. For larger children of more than 20 kg, where four or more sprays of the 5-mg ml^{-1} solution were needed, compliance was a real problem and movement and struggling between sprays led to loss of some of the solution. This was even more noticeable as the stinging was apparent immediately. A more concentrated solution would have allowed fewer sprays, but this could not be formulated through our pharmacy department, although a 40-mg ml^{-1} solution was used in one other study.[30] Transmucosal absorption depends on the physical and chemical properties of a solution; better absorption may be expected if midazolam was in a lipophilic vehicle at neutral pH unlike the hydrophilic form in which it exists. Secretions from nasal irritation may also alter absorption.

We used a four-point scoring system modified from Davis and colleagues.[14] This was limited in that it allowed only two extreme scores and two intermediate scores. Also, the statistical analysis assumed that the points were evenly distributed on an interval scale. While we used a scoring system which had been used previously by other authors, a visual analogue scale would have helped obviate these problems. The difficulties with behavioural scoring systems are reflected by the fact that, while the scoring system showed that parents scored their child as more distressed in theatre, from the parental questionnaire, 36 of 44 parents felt that their child's behaviour had improved by the time they arrived in theatre. Also, the case anaesthetist and recovery nurses felt that behaviour was good in the majority of children (table 1). This may reflect the subtle distinction between distress and behaviour. A child may be well behaved but terrified. However, it seems likely that our current tools for measuring distress in children are not perfect.

The study was not fully blinded as the logistics were such that the study anaesthetist also administered the premedication and therefore could not be blinded. Only the nurse was blinded to the route of premedication as it was considered to be unacceptable to exclude the parent from the room at that time. There was no placebo group as inclusion of such a group would have complicated the study design, but it would have allowed the efficacy of nasal midazolam by different applicators to be examined quantitatively.

In summary, midazolam was shown to cause significant distress at the time of intranasal administration, whether by drops or spray. This is subsequently remembered by children as an unpleasant experience and thus it cannot be recommended as a routine method of premedication in children.

References

1. Allonen H, Ziegler G, Klotz U. Midazolam kinetics. *Clinical Pharmacology and Theraputics* 1981; **30**: 653–661.
2. Payne K, Mattheyse FJ, Linenberg D, Dawes T. The pharmacokinetics of midazolam in paediatric patients. *European Journal of Clinical Pharmacology* 1989; **37**: 267–272.
3. Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. *Anesthesiology* 1990; **73**: 831–834.
4. Saint-Maurice C, Meistelman C, Rey E, Esteve C, De Lauture D, Olive G. The pharmacokinetics of rectal midazolam for premedication in children. *Anesthesiology* 1986; **65**: 536–538.
5. Spear RM, Yaster M, Berkowitz ID, Maxwell LG, Bender KS, Naclerio R, Manolio TA, Nichols DG. Preinduction of anesthesia in children with rectally administered midazolam. *Anesthesiology* 1991; **74**: 670–674.
6. Karl HW, Rosenberger JL, Larach MG, Ruffle JM. Transmucosal administration of midazolam for premedication of pediatric patients (comparison of the nasal and sublingual route). *Anesthesiology* 1993; **78**: 885–891.
7. Wilton NC, Leigh J, Rosen DR, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology* 1988; **69**: 972–975.
8. Walberg EJ, Wills RJ, Eckhert J. Plasma concentrations of midazolam in children following intranasal administration. *Anesthesiology* 1991; **74**: 233–235.
9. Rey E, Delaunay L, Pons G, Murat I, Richard M, Saint-Maurice C, Olive G. Pharmacokinetics of midazolam in children—comparative study of intranasal and intravenous administration. *European Journal of Clinical Pharmacology* 1991; **41**: 355–357.
10. Bjorkman G, Rigemar G, Idvall J. Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients. *British Journal of Anaesthesia* 1997; **79**: 575–580.
11. Houi N, Boishardy N, Chapotte C, Granry JC, Delhumeau A. Premedication par le midazolam chez l'enfant. *Cahiers d'Anesthesiologie* 1992; **40**: 167–170.
12. Malinovsky J-M, Populaire C, Cozian A, Lepage J-Y, Lejus C, Pinaud M. Premedication with midazolam in children. Effect of intranasal, rectal and oral routes on plasma midazolam concentrations. *Anaesthesia* 1995; **50**: 351–354.
13. Rose E, Simon D, Haberer JP. Premedication par midazolam intranasal en anesthesie pediatrique. *Annals Francais d'Anesthesie et Reanimation* 1990; **9**: 326–330.
14. Davis PJ, Tome JA, McGowan FX, Cohen IT, Latta K, Felder H. Preanesthetic medication with intranasal midazolam for brief pediatric surgical procedures. *Anesthesiology* 1995; **82**: 2–5.
15. *Stata 5 Reference Manual—User's Guide, Release 5*. Texas: Stata Press, 10; 235–239.
16. Vetter TR. The epidemiology and selective identification of children at risk for preoperative anxiety reactions. *Anesthesia and Analgesia* 1993; **77**: 96–99.
17. Twersky RS, Hartung J, Berger BJ, McCain J, Beaton C. Midazolam enhances anterograde but not retrograde amnesia in pediatric patients. *Anesthesiology* 1993; **78**: 51–55.
18. Payne KA, Coetzee AR, Mattheyse FJ, Midazolam and amnesia in paediatric premedication. *Acta Anaesthesiologica Belgica* 1991; **42**: 101–105.
19. McCluskey A, Meakin GH. Oral administration of midazolam as a premedicant for paediatric day-case anaesthesia. *Anaesthesia* 1994; **49**: 782–785.
20. Karl HW, Keifer AT, Rosenberger JL, Larach MG, Ruffle MD. Comparison of the safety and efficacy of intranasal midazolam and sufentanil for preinduction of anesthesia in pediatric patients. *Anesthesiology* 1992; **76**: 209–215
21. Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anaesthesia: a comparison of midazolam and ketamine. *Canadian Journal of Anaesthesia* 1994; **41**. 3: 221–226.
22. De Guio G, Bartier JC. Quelle sedation pour la petite chirurgie traumatique chez l'enfant? *Archives Pediatriques* 1994; **1**: 515–518.
23. Malinovsky J-M, Lejus C, Servin F, Lepage J-Y, Le Normand Y, Testa S, Cozian A, Pinaud M. Plasma concentrations of midazolam after i.v., nasal or rectal administration in children. *British Journal of Anaesthesia* 1993; **70**: 617–620.
24. Stanley TH. New routes of administration and new delivery systems in anesthetics. *Anesthesiology* 1988; **68**: 665–668.
25. Fuks AB, Kaufman E, Ram D, Hovav S, Shapira J. Assessment of two doses of intranasal midazolam for sedation of young pediatric dental patients. *Pediatric Dentistry* 1994; **16**: 301–305.
26. Slover R, Dedo W, Schlesinger T, Mattison R Use of intranasal midazolam in preschool children. *Anesthesia and Analgesia* 1990; **70**: S377.
27. Mitchell V, Grange A, Black A, Train J. A comparison of midazolam with trimeprazine as an oral premedicant for children. *Anaesthesia* 1997; **52**: 416–421.
28. Foesl T, Hack C, Knoll R, Kraus GB, Larsen R. Nasal midazolam in children, plasma concentrations and the effect on respiration. *Paediatric Anaesthesia* 1995; **5**: 347–353
29. Hodgson PE, Woods KM, Bromley LM. Administration of nebulised intranasal midazolam to healthy volunteers: a pilot study. *British Journal of Anaesthesia* 1994; 73 (Suppl.): 719P
30. Fukuta O, Braham RL, Yanase H, Atsumi N, Kuroso K. The sedative effect of intranasal midazolam administration in the dental treatment of patients with mental disabilities. *Journal of Clinical Pediatric Dentistry* 1993; **17**: 231–237.

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I.v. intraoperative ketoprofen in small children during adenoidectomy: a dose-finding study

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Summary

We have investigated if a low dose of ketoprofen (0.3 mg kg^{-1}) i.v., provided as good analgesia with less adverse effects than higher doses (1.0 and 3.0 mg kg^{-1}) in 220 children, aged 1–7 yr, undergoing adenoidectomy, in a prospective, randomized, double-blind, placebo-controlled, parallel group study. The postoperative analgesic effect was notable even after the lowest dose of ketoprofen. However, the higher doses seemed to provide better analgesia with no increase in adverse events or intraoperative bleeding. None of the children experienced postoperative bleeding which would have required intervention or delayed discharge from hospital. This study confirms the efficacy and safety of intraoperative ketoprofen in children during adenoidectomy. (*Br. J. Anaesth.* 1998; **81**: 870–874).

Keywords: pain, postoperative; analgesics non-opioid, ketoprofen; analgesia, pre-emptive; analgesia, paediatric; surgery, otolaryngological

After day-case surgery, children need to be free from pain and alert when leaving hospital. Analgesia should be initiated with an effective drug which has few adverse effects. Opioids, although potent analgesics, can produce emesis, excessive sedation and respiratory depression. Non-steroidal anti-inflammatory drugs (NSAID) can eliminate the need for opioids after operation in children.[1] However, NSAID can cause gastrointestinal and renal dysfunction. They also prolong the bleeding time and so can increase postoperative blood loss.[2]

Ketoprofen is a NSAID which belongs to the same group of phenylpropionic acid derivatives as ibuprofen and naproxen. It has been in clinical use since 1974.[3] In many countries, ketoprofen is available for i.v. administration; this may be useful during the intraoperative period. Adenoidectomy is one of the most common surgical procedures in childhood and it is frequently carried out as a day-case procedure. In our previous studies, we have proved that intraoperative ketoprofen i.v. provides good background analgesia with a low incidence of adverse effects after adenoidectomy in small children.[4 5] To date, the optimal dose of ketoprofen for children in the treatment of postoperative pain is unknown.

In this study, we have determined if a low dose of ketoprofen i.v. provided good analgesia with less adverse effects than higher doses in children aged 1–7 yr after adenoidectomy. Doses of ketoprofen 0.3, 1.0 and 3.0 mg kg^{-1} were compared with placebo; doses of 0.3 mg kg^{-1} and 3.0 mg kg^{-1} have not been studied previously. It was of interest to see if this high dose would enhance efficacy without increasing adverse effects.

Patients and methods

The study was approved by the Ethics Committee of Kuopio University Hospital and was conducted in accordance with the Declaration of Helsinki. The parents of all patients gave written informed consent. The National Agency for Medicine approved the use of ketoprofen in children less than 20 kg.

We studied 220 ASA I–II patients, aged 1–7 yr, undergoing adenoidectomy (with or without myringotomy, tympanostomy or sinus lavage). Patients were excluded if they had a known allergy to ketoprofen or any other NSAID, asthma, kidney or liver dysfunction, or a haemorrhagic diathesis. We used a prospective, randomized, double-blind, placebo-controlled, parallel group study design. Children were allocated randomly to one of three ketoprofen groups or a placebo group. Fentanyl i.v. was available for rescue analgesia. A block randomization method was used to keep the number of children equal in all groups. After induction of anaesthesia, children in the ketoprofen groups received ketoprofen 0.3 mg kg^{-1} (group 0.3), 1.0 mg kg^{-1} (group 1.0) or 3.0 mg kg^{-1} (group 3.0) dissolved in 10 ml of 0.9% saline, injected i.v. over 5 min. Children in the placebo group received a similar volume of 0.9% saline. The number of children in each group was 55.

A standard anaesthetic technique was used. Each child was premedicated with diazepam 0.5 mg kg^{-1} orally up to a maximum of 10 mg, 30–45 min before induction of anaesthesia. EMLA cream (Astra, Sweden) was applied to the skin 60 min before venepuncture. Anaesthesia was induced with thiopental (thiopentone) 5–7 mg kg^{-1} and fentanyl 1 µg kg^{-1}, and tracheal intubation was facilitated with atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained with 1–1.5% isoflurane (inspired concentration) and 65% nitrous oxide in oxygen with IPPV. On completion of the procedure, neuromuscular block was

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antagonized with neostigmine 50 μg kg^{-1} and glycopyrrolate (glycopyronnium) 10 μg kg^{-1}. No more opioid was given during operation after the induction dose of fentanyl. All children were given 0.9% saline 10 ml kg^{-1} h^{-1} for intraoperative fluid maintenance. After surgery, children were transferred to the post-anaesthesia care unit (PACU) for continuous monitoring of vital signs and assessment of pain.

The adenoids were removed using a curettage technique. Haemostasis was controlled with temporary nasopharyngeal packs with or without electrocautery. Surgeons estimated the amount of bleeding using a five-point scale (1=no bleeding, 2=less than normal, 3=normal, 4=more than normal and 5=profuse).

Postoperative pain was assessed using the Maunuksela score.[6] The Maunuksela score is an observer assessment based on facial expression, vocalization, movement or rigidity of the limbs and body, response to handling and irritability, and measured cardiorespiratory variables. In the Maunuksela score, 0=no pain, 1–3=mild pain, 4–6=moderate pain, 7–9=severe pain and 10=worst possible pain.

Specially trained research nurses assessed pain expressed by the child at rest and during swallowing. Pain scores were recorded hourly. If the child was in pain at rest (pain score ≥3) fentanyl 1 μg kg^{-1} was given for rescue analgesia and was repeated at 10-min intervals until the child was comfortable. No more than three doses of fentanyl were allowed in 1 h. No other analgesic medication was permitted during the study. The children were monitored closely after each dose of fentanyl in the PACU. Just before leaving hospital, pain at rest and during swallowing was assessed and recorded. At the same time, the worst pain during the PACU stay was noted. All adverse events were recorded for each patient.

The children were discharged when vital signs were stable, they were awake or easily aroused, had no pain or mild pain, were able to tolerate clear fluids, had no bleeding and had not vomited for 60 min. On discharge, all children received a ketoprofen tablet (2 mg kg^{-1}) and, for postoperative pain relief at home, all children were given ketoprofen 25-mg tablets and instructed to take 2 or 3 tablets per day (5 mg kg^{-1} day^{-1}).

A power analysis suggested that to have an 80% chance of obtaining a 30% reduction in the need for rescue analgesia at an α-level of 0.05, a minimum of 48 children per group would be needed. As the data were not normally distributed, analysis of continuous variables was performed using the Kruskal–Wallis test, and for *post hoc* analysis, the Mann–Whitney test with Bonferonni correction was used. For categorical variables the chi-square test was used. *P*≤0.05 was considered statistically significant. Results are presented as number of cases (%) or median (10th and 90th) percentiles, as appropriate.

Results

Sex distribution, age, weight, height and ASA status were similar in the four groups (table 1).

The number of children who needed fentanyl in the PACU was smallest in group 3.0 and significantly different compared with the placebo group (*P*=0.01). In the placebo group, 45 (82%) children were given fentanyl compared with 36 (65%), 34 (62%) and 29 (53%) in groups 0.3, 1.0 and 3.0, respectively. The number of fentanyl doses needed in the PACU was smaller in all ketoprofen groups compared with the placebo group (*P*=0.01–0.001). The number of children who needed more than two fentanyl doses in the PACU was significantly less in all ketoprofen groups (*P*=0.018–0.001) compared with the placebo group. There was no significant difference between the ketoprofen groups (fig. 1).

Of those children who were administered fentanyl in the PACU, fewer doses were needed in group 1.0 (*P*=0.029) and group 3.0 (*P*=0.003) compared with the placebo group. The proportion of children who were administered more than two doses of fentanyl was less in group 1.0 (*P*=0.033) and group 3.0 (*P*=0.006) compared with the placebo group.

Time to the first dose of fentanyl in the PACU was longer in the ketoprofen groups than in the placebo group, but this difference was not statistically significant (*P*=0.08): 22 (10th and 90th percentiles 8–57) min in the placebo group and 27 (10–73) min, 33 (13–76) min and 30 (16–82) min in groups 0.3, 1.0 and 3.0, respectively.

Maunuksela pain scores observed during swallowing, 2 h after surgery, were lower in group 3.0 compared with the placebo group (*P*=0.046). The worst pain at rest in the PACU was also lower in group 3.0 compared with the placebo group (*P*=0.014) (table 2).

The surgeon estimated the amount of intraoperative bleeding using a five-point scale. Although children in group 0.3 were estimated to bleed more than children in the placebo group, the difference was not significant (*P*=0.055) (table 3). One child in group 3.0 had epistaxis in the PACU but it stopped without intervention. No child experienced postoperative bleeding which would have required intervention or reoperation, or which would have caused delay in discharge from hospital.

In the PACU, there were no differences in the incidence or distribution of adverse effects between groups (table 4). There were no serious adverse

Table 1 Patient data for the four study groups (median (10th and 90th percentiles) or number)

		Ketoprofen		
	Placebo (*n*=55)	Group 0.3 (*n*=55)	Group 1.0 (*n*=55)	Group 3.0 (*n*=55)
Sex (M/F)	28/27	34/21	32/23	33/22
Weight (kg)	15 (11–24)	15 (11–25)	14 (11–23)	14 (10–24)
Height (cm)	98 (80–123)	96 (81–120)	92 (78–125)	92 (79–118)
Age (months)	41 (15–79)	40 (18–74)	32 (15–85)	32 (15–72)
ASA (I/II)	55/0	52/3	52/3	52/3

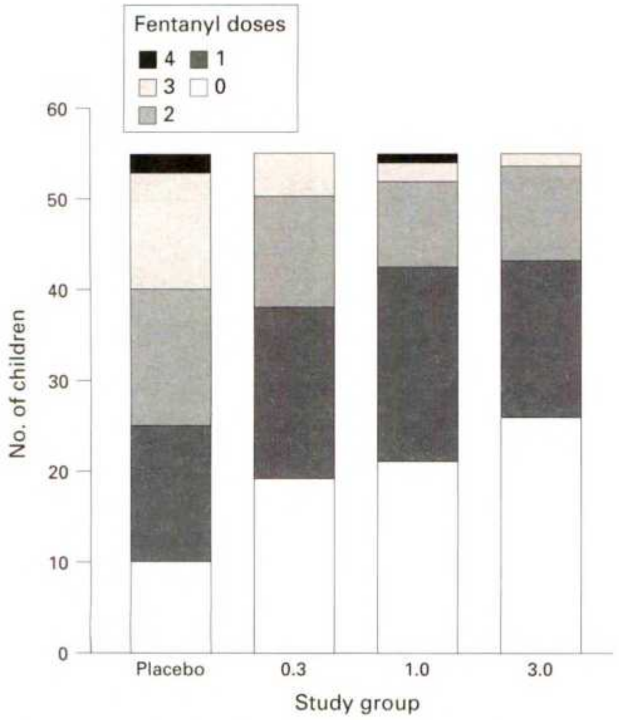

Figure 1 Number of fentanyl doses during the first 2 h in the post-anaesthesia care unit in the ketoprofen groups (ketoprofen 0.3 mg kg^{-1} (group 0.3), 1.0 mg kg^{-1} (group 1.0) and 3.0 mg kg^{-1} (group 3.0)) and in the placebo group. Placebo *vs* group 0.3, $P=0.01$; placebo *vs* group 1.0 and group 3.0, $P=0.001$ (Mann–Whitney test with Bonferroni correction).

events and the medication was not discontinued in any patient.

Administration of fentanyl had an impact on the incidence of adverse effects and episodes of vomiting. Seven children (9%) who did not receive fentanyl in the PACU had adverse effects compared with 30 children (21%) who did ($P=0.012$). The number of vomiting episodes was four of 76 children who did not receive fentanyl and 19 of 144 children who did ($P=0.032$). Those children who did not receive fentanyl had lower pain scores during swallowing (0(0–1)) on leaving hospital than those who were given fentanyl (0(0–2)) in the PACU ($P=0.035$).

Discussion

In this study, we have shown that the use of ketoprofen reduced the number of doses of fentanyl needed in the PACU. The proportion of children who needed fentanyl in the PACU was also smaller if they had received ketoprofen. The differences were statistically significant after a dose of ketoprofen 3.0 mg kg^{-1} compared with placebo, but the tendency was present after the smaller doses. Further, in those children who required fentanyl, the number of fentanyl doses was smaller if ketoprofen had been administered. Our data suggest that ketoprofen i.v. provides effective background analgesia with all of the doses used in this study. It also has a significant opioid-sparing effect. The analgesic effect was enhanced with the higher doses, but even the smallest dose had a significant effect in reducing the requirement for fentanyl.

In this study, we used a placebo-controlled method. The use of a placebo group was ethical as all children in pain were administered fentanyl for rescue analgesia, and before discharge all children receive a ketoprofen tablet (2 mg kg^{-1}). The worst pain at rest in the PACU was assessed as less in those children who had received a high dose of ketoprofen. These children also experienced less pain during swallowing 2 h after operation. This difference was not seen 1 h after operation. The relatively slow onset of analgesic effect has also been shown in previous studies with ketoprofen and other analgesics which act via inhibition of prostaglandin synthesis.[1 3 7]

NSAID are known to prolong bleeding time by inhibiting cyclo-oxygenase which leads to inhibition of platelet thromboxane A2 production and platelet aggregation.[2] Perioperative ketorolac has been studied widely in the treatment of postoperative pain in children. Increased perioperative bleeding has been shown to occur with ketorolac 1 mg kg^{-1}.[1 8 9] In our previous studies with ketoprofen, only one child experienced postoperative bleeding.[4 5] This child received ketoprofen 2.0 mg kg^{-1} and was observed for a few hours before discharge. In none of our three studies of 491 children has postoperative bleeding occurred which would have required intervention or overnight admission to hospital. These results may indicate the

Table 2 Maunuksela pain scores in the post-anaesthesia care unit (PACU) (median (10th and 90th percentiles)). *$P=0.046$, **$P=0.014$ (Mann–Whitney test) between the placebo group and group 3.0

		Ketoprofen			
	Placebo (*n*=55)	Group 0.3 (*n*=55)	Group 1.0 (*n*=55)	Group 3.0 (*n*=55)	*P* Kruskal–Wallis
After 1 h					
At rest	1 (0–8)	0 (0–8)	0 (0–8)	0 (0–8)	0.357
Swallowing	4 (0–8)	3 (0–8)	1 (0–8)	1 (0–9)	0.457
After 2 h					
At rest	0 (0–6)	0 (0–5)	0 (0–1)	0 (0–5)	0.091
Swallowing	1 (0–7)	0 (0–7)	0 (0–4)	0 (0–6)*	0.047
On leaving the PACU					
At rest	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0.613
Swallowing	0 (0–1)	0 (0–3)	0 (0–2)	0 (0–1)	0.132
Worst pain in the PACU					
At rest	4 (0–8)	3 (0–8)	2 (0–8)	1 (0–8)**	0.026
Swallowing	5 (0–8)	4 (0–8)	3 (0–8)	3 (0–8)	0.059

Table 3 Intraoperative bleeding estimated by the surgeon (*n* (%))

	Placebo (*n*=55)	Ketoprofen Group 0.3 (*n*=55)	Group 1.0 (*n*=55)	Group 3.0 (*n*=55)
Less than normal	5 (9)	1 (2)	0 (0)	2 (4)
Normal	47 (86)	45 (82)	53 (96)	50 (91)
More than normal	3 (5)	9 (16)	2 (4)	3 (5)

Table 4 Number of adverse effects in the post-anaesthesia care unit (*n* (%))

	Placebo (*n*=55)	Ketoprofen Group 0.3 (*n*=55)	Group 1.0 (*n*=55)	Group 3.0 (*n*=55)
Vomiting and/or nausea	5 (9)	5 (9)	4 (7)	5 (9)
Epigastric distress	—	—	1 (2)	—
Somnolence	4 (7)	5 (9)	2 (4)	—
Difficulty in passing urine	1 (2)	1 (2)	—	—
Sa_{O_2} <90%	—	—	1 (2)	—
Redness at the puncture site	—	1 (2)	—	—
Mild epistaxis	—	—	—	1 (2)
Agitated	—	1 (2)	—	—
Total No. of adverse reactions	10	13	8	6
No. of children with one or more adverse reactions	9 (16)	12 (22)	5 (9)	6 (11)

different effects of NSAID on platelet function and are worthy of further study.[10] Inhibition of maximal platelet aggregation and platelet thromboxane synthesis has been shown to be dose related with ketoprofen and ibuprofen.[11] In our previous study, intraoperative bleeding was estimated to be greater in children who received ketoprofen 2 mg kg^{-1} than in those who received placebo.[4] In the present study, only children who received ketoprofen 0.3 mg kg^{-1} had slightly more intraoperative bleeding compared with those who received placebo. This difference was not seen after ketoprofen 1.0 or 3.0 mg kg^{-1}. Therefore, the tendency to dose related intraoperative bleeding was not seen in our studies. However, in our studies, intraoperative bleeding was estimated by the surgeon using a five-point scale. Obviously, this method may neglect minor differences in intraoperative bleeding and more exact methods should be used in future studies.

In previous studies with ketoprofen, the incidence of adverse effects varied from 0% to 50%.[3] In our study, 14% of children receiving ketoprofen and 16% of children receiving placebo had one or more adverse effects. There were no serious adverse events. The incidence and scale of adverse effects in our study were comparable with earlier reports of short-term use of NSAID in children.[4,5,7] Based on this study and earlier studies, we can confirm the safety of i.v. ketoprofen in children during adenoidectomy.

In day-case surgery in children, it is necessary that parents feel safe to leave hospital with their child. Children should therefore be painfree and alert. Pain and nausea and vomiting are common problems after adenotonsillar surgery in children and can delay discharge.[12,13] In this study, children had less vomiting and fewer adverse effects if they were not given fentanyl in the PACU. Pain scores were minimal in all groups by discharge. However, on leaving hospital, children who were not given fentanyl had even lower pain scores during swallowing. These results support the use of NSAID in day-case surgery in children because of their opioid-sparing effect.[1]

In our studies, we have used intraoperative ketoprofen i.v. doses of 0.3–3.0 mg kg^{-1}.[4,5] For routine use, we recommend a dose of 1 mg kg^{-1}. The higher ketoprofen doses seem to provide better analgesia without any increase in adverse effects or perioperative bleeding. Hence when severe postoperative pain is expected after surgery, higher doses or repeated doses can be used safely. On the other hand, even the lowest doses seem to provide effective background analgesia. This finding should be considered in children undergoing surgery accompanied by a higher risk of intraoperative bleeding and in children who are expected to have any reduction in haemostatic function. In children with a high risk of bleeding, it is appropriate to use alternative agents (e.g. paracetamol).

In our opinion, based on this and our previous studies,[4,5] ketoprofen i.v. is a potent analgesic for use in children undergoing day-case surgery. It provides effective background analgesia after adenoidectomy without any adverse effects or perioperative bleeding.

References

1. Romsing J, Walther-Larsen S. Peri-operative use of nonsteroidal anti-inflammatory drugs in children: analgesic efficacy and bleeding *Anaesthesia* 1997; **52**: 673–683.
2. Maunuksela E-L. Nonsteroidal anti-inflammatory drugs in pediatric pain management. In: Schechter NL, Berde CB, Yaster M, eds. *Pain in Infants, Children and Adolescents* Baltimore: Williams and Wilkins, 1993, 135–143.
3. Fossgreen J. Ketoprofen. *Scandinavian Journal of Rheumatology* 1976, (Suppl 14): 11–31
4. Nikanne E, Kokki H, Tuovinen K. I.v. perioperative ketoprofen in small children during adenoidectomy. *British Journal of Anaesthesia* 1997, **78**: 24–27.
5. Nikanne E, Kokki H, Tuovinen K. Comparison of a dose of 2.0 mg kg^{-1} with a dose of 0.5 mg kg^{-1} i.v. perioperative ketoprofen in small children during adenoidectomy. *British Journal of Anaesthesia* 1997, **79**: 606–608.

6. Maunuksela E-L, Olkkola KT, Korpela R. Measurement of pain in children with self-reporting and behavioral assessment. *Clinical Pharmacology and Therapeutics* 1987; **42**: 137–141.
7. Maunuksela E-L, Kokki H, Bullingham RES. Comparison of intravenous ketorolac with morphine for postoperative pain in children. *Clinical Pharmacology and Therapeutics* 1992, 52 436–443.
8. Gunter JB, Varughese AM, Harrington JF, Wittkugel EP, Patankar SS, Matar MM, Lowe EE, Myer CM III, Willging JP. Recovery and complications after tonsillectomy in children: A comparison of ketorolac and morphine. *Anesthesia and Analgesia* 1995; **81**: 1136–1141.
9. Splinter WM, Rhine EJ, Roberts DW, Reid CW, MacNeill HB. Preoperative ketorolac increases bleeding after tonsillectomy in children. *Canadian Journal of Anaesthesia* 1996, **43**: 560–563.
10. Niemi TT, Taxell C, Rosenberg PH. Comparison of the effects of intravenous ketoprofen, ketorolac and diclofenac on platelet function in volunteers. *Acta Anaesthesiologica Scandinavica* 1997; **41**: 1353–1358.

11 Stichtenoth DO, Tsikas D, Gutzki F-M, Frölich JC. Effects of ketoprofen and ibuprofen on platelet aggregation and prostanoid formation in man. *European Journal of Clinical Pharmacology* 1996; **51**: 231–234.

12. Karlsson E, Larsson LE, Nilsson K. Postanaesthetic nausea in children. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 515–518.
13. Hamid SK, Selby IR, Sikich N, Lerman J. Vomiting after adenotonsillectomy in children: a comparison of ondansetron, dimenhydrinate and placebo. *Anesthesia and Analgesia* 1998; **86**: 496–500.

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Tenoxicam and paracetamol–codeine combination after oral surgery: a prospective, randomized, double-blind, placebo-controlled study

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Summary

We studied 90 adults undergoing surgical removal of at least both lower third molar teeth as day cases under standardized general anaesthesia. Patients were allocated randomly (with stratification for surgeon) to receive tenoxicam 40 mg, tenoxicam 20 mg or placebo i.v. at induction of anaesthesia and orally (effervescent tablets) with food on each of the subsequent 2 days. Panadeine (paracetamol 500 mg–codeine 8 mg) was given before operation and was available as needed for pain thereafter, to a limit of two tablets every 4 h. Nefopam i.v. was also available. Efficacy variables and adverse reactions were assessed over 6 days. Over the 6-day period, patients who received tenoxicam reported less pain on rest (area under the curve; $P<0.05$) and less disturbance in sleep ($P<0.01$) even though they used fewer Panadeine tablets ($P<0.05$). Differences between tenoxicam 40 mg and 20 mg were not significant. There was no significant difference in nefopam requirements or side effects, and no adverse event attributable to the study medication. (*Br. J. Anaesth.* 1998; **81**: 875–880)

Keywords: anaesthesia, dental; analgesia, postoperative; analgesics non-opioid, tenoxicam; analgesics non-opioid, paracetamol; non-steroidal anti-inflammatory drugs

Pain may last for several days after oral surgery; it is often managed with paracetamol or paracetamol–codeine combinations. Recently, it has become popular for such regimens to be supplemented with non-steroidal anti-inflammatory drugs (NSAID),[1–3] and tenoxicam is well suited for this because it can be administered once a day parenterally or enterally as it has a long half-life (60–70 h).[4] Ketorolac is also suitable for parenteral and enteral administration but it has a short half-life of 4–6 h and needs to be given four times a day.[5] Diclofenac can be used parentally but i.m. administration is associated with muscle damage[6] and i.v. administration causes thrombophlebitis unless the drug is well diluted.[7]

The analgesic efficacy of tenoxicam has been well documented in comparison with placebo in chronic pain and inflammation[4 8] and in several controlled studies in the perioperative setting.[9–27] Those comparing tenoxicam with placebo, saline or no specific treatment have shown no benefit[26] or some combination of reduced consumption of opioids[9 10 12 14 15] or other analgesics,[11] lower pain scores,[10 13] better pain relief and a longer time to request for first analgesia.[10 11] There may be benefit in intra-articular injection,[22 24] or in mixing tenoxicam with local anaesthetic in regional i.v. analgesia,[21 27] but not in local infiltration of the drug.[20 23] Comparisons with other NSAID have shown somewhat similar efficacy,[17 19] although onset of analgesia seems to be slower than with diclofenac.[19 25]

No advantage was demonstrated with tenoxicam 40 mg orally compared with paracetamol 1000 mg orally immediately before oral surgery,[16] and the possibility of benefit from combining paracetamol (with or without codeine) and tenoxicam has not been investigated. Given the side effects of NSAID and the relative safety of paracetamol (with and without codeine),[1] we thought it important to investigate if the practice of adding a NSAID (specifically tenoxicam) provides any additional efficacy to a paracetamol–codeine combination on its own.

The optimal dose of tenoxicam for perioperative analgesia is not clear. A single dose of 20 mg i.v. produces blood concentrations of only 3 mg litre^{-1} compared with more than 10 mg litre^{-1} at steady state with 20 mg daily by mouth.[28] A loading dose would seem rational, given the long half-life of tenoxicam.[4] The manufacturer advises 40 mg daily for 5 days in the context of postoperative pain relief,[29] but Scaglione and colleagues have demonstrated that single 40-mg loading doses for 2 days, followed by once-daily 20-mg maintenance administration established the requisite steady-state tissue concentration of tenoxicam after the second administration.[30]

Therefore, the aim of this study was to investigate the efficacy of tenoxicam 20 and 40 mg when used with up to two tablets of Panadeine (paracetamol 500mg–codeine 8 mg) every 4 h, for pain after oral surgery.

Patients and methods

This study was undertaken between June 2, 1993 and May 25, 1994. Approval of the regional Ethics Committee and written informed consent from all patients were obtained. In order to have a statistical power of 80% to show a difference between groups of 25 mm on a 100-mm visual analogue scale (VAS), assuming an SD of 30 mm and nominating $P<0.05$ as significant,[31] 90 patients were recruited.

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Patients were included if they were undergoing surgical removal of at least both lower wisdom teeth (with or without extraction of one or two upper wisdom teeth), under general anaesthesia in a day-stay facility. Exclusion criteria were: hypersensitivity to aspirin or other NSAID; asthma; history of peptic ulceration, gastrointestinal bleeding or any bleeding disorder; presence of severe renal impairment (creatinine $\geq$0.2 mg ml^{-1}), hepatic, cardiac or haemopoietic disease; pregnancy; presence of any neurological disorder liable to interfere with perception of pain; history of drug addiction; presence of severe local infection; current use of another experimental agent; previous general anaesthetic within 6 months; and use of NSAID, opioids, diuretics or angiotensin converting enzyme inhibitors in the 24 h preceding surgery.

Anaesthesia was induced with a sleep dose of propofol and maintained with halothane and nitrous oxide in oxygen. Patients breathed spontaneously via a nasal airway or a laryngeal mask, with appropriate packing of the oropharynx. All patients received amoxycillin or erythromycin (if allergic to amoxycillin) before and after surgery. No opioids were given. Monitoring was in accordance with the guidelines of the Australian and New Zealand College of Anaesthetists (ANZCA).[32]

All extractions were carried out by one of two surgeons who used a standardized technique, except that local anaesthetic blocks with 2% lidocaine (lignocaine) with epinephrine (adrenaline) 1:80 000 were used by one (J. E.) but not the other (P. S.), in accordance with normal practice. They rated the difficulty of the extraction in each case.

Patients were allocated randomly, in blocks of 15 with stratification for surgeon, to receive tenoxicam 40 mg, 20 mg or placebo (groups T40, T20 and PG, respectively). The medication was given i.v. immediately after induction of anaesthesia and orally (as effervescent tablets dissolved in water) with food (at breakfast) on days 1 and 2 (the day of surgery being day 0). The study was double-blind, with no access to the codes, other than by a formalized contingency protocol, until all data had been entered into the computer and verified against a subset re-entered by a second person. No interim analysis was undertaken.

Two tablets of Panadeine (paracetamol 500 mg with codeine 8 mg) were given 45 min before operation to provide basal analgesia. Panadeine tablets were available on an "as required" basis after operation up to a maximum of two tablets 4-hourly. Consumption over days 0–5 was monitored and checked against medication at the end. Nefopam 20 mg i.v. (repeated once if necessary) was also available while in hospital for severe pain.

The primary outcome variable was pain, which was assessed using a 100-mm unmarked visual analogue scale (VAS) with the anchors "no pain" and "severe pain". Patients indicated their "present pain" in hospital 1 h after operation (day 0) and daily (including the day of discharge) at approximately 18:00 (days 0a–5). Each of the latter scores were marked by the patient on a separate VAS included as part of individual pages of a diary. Patients were also asked to assess their pain on a VAS immediately before operation. A daily follow-up telephone call to each patient was made on days 0–6 by the study nurse at approximately 18:00 as a reminder to record their present pain on that day's VAS and to ask about any adverse events which were recorded. At the day 1 telephone call, a categorical rating (as "nil", "mild", "moderate" or "severe", recorded as 0–4) was obtained for pain experienced over the first 24 h after surgery. A similar rating of sleep disruption during the preceding night, attributed by the patient to pain, was obtained at every telephone call from day 1 onwards. Panadeine consumption was also recorded daily. While the patient was in hospital, the study nurse also recorded the following: heart rate, ventilatory frequency and arterial pressure (before and after surgery); sedation rating, nausea rating, vomiting, consumption of antiemetic medication and use of rescue nefopam (after surgery). During the last telephone interview, she asked patients to rate the experience of taking part in the study. Patients were assessed at clinic by the surgeon after 7 days. Haemoglobin and creatinine concentrations were measured during operation and at the routine follow-up. Any adverse event was allocated a severity rating jointly by two investigators according to a standard protocol developed by Roche Products. The investigators judged the relationship between these events and the study drug as definite, possible or probable, but all events were recorded to ensure that no events were inappropriately suppressed.

The processes involved with data collection were twice subjected to formal audit by a person not associated with the study. Patients received a small payment (NZ$100) to defray the expense associated with attending a laboratory for the second blood sample and to acknowledge the inconvenience of taking part in the study.

Area under the curve (AUC_{0-5}) of the pain VAS (in mm days) for each patient was calculated for days 0–5 starting from 1 h after operation. Panadeine consumption (in tablets) and sleep disturbance scores were summed for days 0–5. Categorical ratings of pain over the first 24 h and VAS at 18:00 on the day of surgery (day 0a) were analysed separately as indicators of early efficacy. None of these variables was normally distributed, even after logarithmic and other transformations were performed, and therefore all efficacy data were analysed using the non-parametric Kruskal–Wallis ANOVA, unless otherwise stated. For each variable, the planned orthogonal contrasts (PG *vs* the combined tenoxicam groups and T40 *vs* T20) were calculated when the treatment main effect was significant (specified as $P \leq 0.05$). Repeated measures ANOVA was used to examine differences between groups in changes between preoperative and postoperative values of haemoglobin, creatinine, heart rate, ventilatory frequency and arterial pressure. All *P* values are reported without correction.

Results

We screened 143 patients. An ampoule of study medication was opened for a recruited patient who did not attend, and therefore 89 patients took part in the study. The reasons for the other exclusions are listed in table 1. There were no other withdrawals and no early code breaks.

Table 1 Reasons for excluding patients from the study (143 were screened in total)

Reason for exclusion from study	Total
Administrative	
Nurse or anaesthetist unavailable	5
Patient cancelled appointment for operation	7
Patient would not be available for 7 day follow-up	3
Patient declined	
Did not want a placebo	3
Feared blood test	14
Preferred other drug	1
Disliked drugs generally	2
Feared side effects, anxious	4
Family unwilling	1
Did not want to complete a diary	1
Study contraindications	
Too young or too old	5
GA within 6 months	2
Unable to take effervescent form of medication	1
NSAID contraindications	
Severe known haemopoietic disease	1
Hypersensitive to aspirin or other NSAID	4
Total excluded	54

Table 2 Patient characteristics (mean (SD or range) or number)

	Placebo group	T20 group	T40 group
n	29	30	30
Age (yr)	22.1 (18–28)	22.2 (18–28)	21.6 (18–30)
Weight (kg)	66.0 (2.0)	70.5 (2.0)	66.3 (2.1)
Duration of surgery (min)	24.9 (2.0)	22.9 (2.0)	21.6 (2.0)
Sex (F:M)	15:14	12:18	10.20

Treatment groups were similar in age, ethnic group, concomitant medication and secondary diagnosis, but weight and sex were less evenly distributed (table 2). Seventy-five patients had no preoperative pain; the remainder were well distributed between the three groups.

Six patients required nefopam in the immediate postoperative period: four in the T40 group and one each in groups T20 and PG (Fisher's exact test; ns). There was no significant difference between groups or surgeons for extraction difficulty or duration of operation. Minor discrepancies in Panadeine consumption, identified by checking returned tablets, were similar between groups. Analysis on the basis of returned tablets gave essentially identical results to those reported below.

Males had higher pain scores than females but this difference was not significant (P=0.4; median scores for AUC_{0-5} were 132.4 and 100.9 mm days, respectively).

There was no significant difference between surgeons for any outcome variable, except in the first hour after operation, when pain scores favoured the surgeon who used local anaesthetic (median 10 (interquartile range 2, 37) and 43 (26, 58) for rest pain VAS and 8 (2, 44) and 45 (28, 59) for pain on talking VAS, respectively; P<0.01). This was not the case, however, for the categorical assessment of overall pain for the first day (P=0.86) or for pain scores at rest at 18:00 on the day of surgery (P=0.66).

There was a significant difference in pain at rest AUC_{0-5} between the three groups: median 167.7 (interquartile range 94.5, 257.5), 89.9 (43.8, 140.7) and 86.9 (41.3, 184.8) mm days for groups PG, T20 and T40, respectively (P=0.04). This was attributable to a significant advantage for the combined tenoxicam groups compared with the placebo group (P=0.016) but there was no significant difference between groups T20 and T40 (fig. 1). The significant advantage for the combined tenoxicam groups persisted for days 0–3 (table 3).

There was a significant difference in: total Panadeine consumption over days 0–5 for the three groups (fig. 2) (median 28 (interquartile range 13, 33), 16 (8, 30) and 16 (8, 23) for groups PG, T20 and T40, respectively (P=0.024); rest pain VAS at 18:00 on the day of surgery (P=0.01, table 3); verbal pain rating for the first 24 h after surgery (median 3 (interquartile range 3, 3), 2 (2, 3) and 3 (2, 3) for groups PG, T20 and T40, respectively (P=0.02); and total sleep disturbance scores for days 0–5 (median 9 (interquartile range 8, 12), 7 (6, 9) and 8 (6, 9) for groups PG, T20 and T40, respectively (P=0.01). These were attributable in each case to a highly significant advantage (P<0.01) for the combined tenoxicam groups compared with the placebo group, with no significant difference between groups T20 and T40. There was no significant difference in pain on talking

Table 3 Median (1st to 3rd quartile range) visual analogue scores (mm) for pain at rest by day for patients receiving placebo (group PG) or tenoxicam 20 mg (group T20) and 40 mg (group T40). On the day of surgery, pain scores were assessed immediately after operation (day 0) and at 18:00 (day 0a)

	PG group	T20 group	T40 group
Day −1	0 (0, 0)	0 (0, 0)	0 (0, 0)
Day 0	43 (24, 55)	29 (8, 50)	33 (20, 49)
Day 0a	53 (29, 64)	34 (20, 52)	25 (15, 46)
Day 1	35 (21, 48)	16 (4, 27)	20 (6, 36)
Day 2	31 (11, 48)	7 (2, 20)	10 (3, 33)
Day 3	20 (5, 40)	6 (0, 21)	7 (2, 36)
Day 4	17 (2, 30)	3 (0, 19)	10 (2, 29)
Day 5	7 (1, 22)	6 (0, 19)	6 (1, 21)

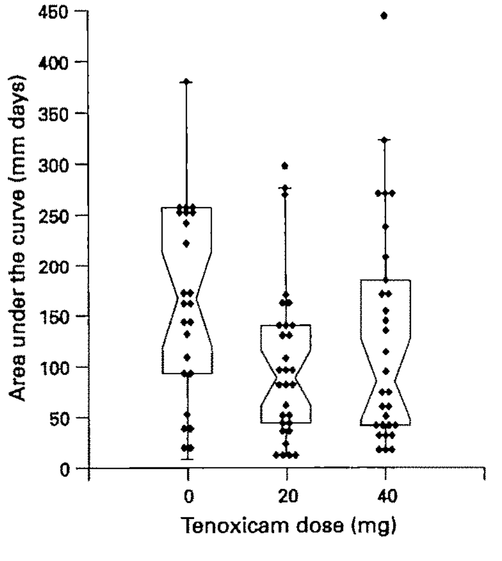

Figure 1 Area under the curve (mm days) for pain at rest visual analogue scales over days 0–5 by dose of tenoxicam (combined scattergram and box and whisker plots, where boxes enclose 1st to 3rd quartiles, whiskers are the highest and lowest values apart from outside values, and notches represent the median and 95% confidence intervals).

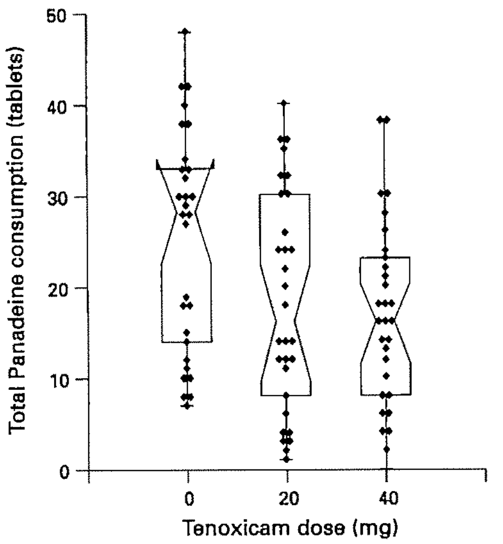

Figure 2 Total Panadeine consumption in tablets over days 0–5 by dose of tenoxicam (combined scattergram and box and whisker plots, where boxes enclose 1st to 3rd quartiles, whiskers are the highest and lowest values apart from outside values, and notches represent the median and 95% confidence intervals).

for any measurement, although the trends were generally in the direction of the significant findings.

Mean haemoglobin concentration decreased for the three groups combined, from 143 (SD 13) g litre^{-1} before operation to 136 (13) g litre^{-1}, 1 week after operation ($P<0.01$), but there was no significant difference between groups. The greatest decrease (from 177 to 156 g litre^{-1}) occurred in a patient who received placebo. Creatinine concentrations showed no significant change over time and no difference between groups. The greatest individual increase (0.03 µmol litre^{-1}) was in a patient who received placebo. Systolic arterial pressure, heart rate and ventilatory frequency did not change significantly after operation and there was no significant difference between groups.

Thirty-eight patients reported a total of 63 adverse events, but no patient had to discontinue treatment because of an adverse effect, no adverse effect persisted beyond 2 days and no significant differences between groups were found (table 4).

Seventy-eight patients rated the experience of taking part in the study as "very positive" or "positive"; 11 considered it "neutral".

Discussion

Patients who received tenoxicam experienced significantly less pain at rest and less disturbance of sleep over the 5 days from the day of surgery than those who received placebo, even though they used significantly fewer Panadeine tablets.

In the tenoxicam groups, patients were heavier, and there was a greater proportion of males and patients who used nefopam. Heavier patients would be expected to have lower plasma concentrations of paracetamol and tenoxicam, and therefore the imbalance in weight seems unlikely to account for our findings. Our males reported slightly higher pain scores overall than females (ns), but this also unlikely to have confounded our results. It is also unlikely that a single dose of the short-acting analgesic nefopam would have had much impact on data amalgamated over 5 days.

Table 4 Adverse events by study group, expressed as number of patients experiencing the event (*n*) and as a percentage (%) of patients in the group, with 95% confidence intervals. Note that the upper 95% confidence limit for those adverse events not actually seen in any given group is 10%, and therefore there is no significant difference between groups for any of these factors. *The three patients who bled more than expected did so on day 0. One patient in the T40 group was graded severe, the other two mild. A surgical cause was identified in each and none was attributed to the study medication by the surgeon. **The column totals exceed the number of patients and differ from the total number of incidents because some patients reported more than one incident; in particular, most who vomited also reported nausea. For the same reason, it is not possible to report total number of incidents as a percentage with confidence intervals because there is no denominator. ***In no patient was the severity sufficient to warrant discontinuation of the medication

	Placebo group (*n*=29)		T20 group (*n*=30)		T40 group (*n*=30)	
	n	%	*n*	%	*n*	%
GI:						
Vomiting	8	28 (13,47)	4	13 (4,31)	7	23 (10,42)
Nausea without vomiting	6	21 (8,40)	30	10 (2,27)	3	10 (2,27)
Stomatitis	1	3 (0, 18)	0		1	3 (0,18)
Constipation	0				1	3 (0,18)
Bleeding*	0		1	3 (0,18)	2	7 (1,22)
Autonomic nervous system						
Sweating	0		0		1	3 (0,18)
Central nervous system						
Headaches						
Sedation	1	3 (0, 18)	1	3 (0,18)	4	13 (4,31)
Skin:						
Pruritus	1	3 (0, 18)	0		0	
No. of patients reporting incidents**	16	53 (34,72)	8	27 (12,46)	14	48 (29,67)
Total number of						
Incidents reported**	23		11		27	
Incidents "possibly" or "probably" related to medication	7		0		7	
Incidents rated as at least "moderately" severe***	15		4		14	

We did not attempt to measure tissue swelling[33] because this would have necessitated repeated clinic visits and because our primary interest was pain relief. We were surprised at the lack of an effect on pain while talking. The principle that pain should be measured during activity and at rest is well established, but it is not quite so obvious what the specific activity should be in the case of oral surgery; perhaps eating would be more relevant.

A loading dose of tenoxicam is pharmacokinetically rational,[28 30] and therefore we were surprised to find no significant difference between the 20-mg and 40-mg doses. Heinaro, Klami and Vaaja also found essentially similar efficacy between 20 mg and 40 mg, in a single oral dose.[17] A dose of 20 mg daily for 3 days, in combination with freely available Panadeine, seems to be effective for pain after oral surgery and the number of patients needed to show a small additional benefit, if present, would be large.

This study was not designed to examine the question of pre-emptive analgesia.[34] However, one surgeon routinely used local anaesthetic before extraction of teeth, and the other did not. As neither was comfortable with modifying his standard practice we resorted to stratification by surgeon to take account of this factor, thus incidentally permitting a comparison of the two approaches, albeit on neither a blinded nor a randomized basis. Pain scores were significantly lower in the local anaesthetic group at 1 h after surgery, when the local anaesthetic was presumably still effective. However, there was no difference in any other outcome variable examined. Even by 18:00 on the day of surgery, no benefit was discernible, and the retrospective assessment of pain for the whole of the first day was not different between groups.

It seems reasonable to conclude that our patients tolerated tenoxicam well in either regimen. No patient discontinued the medication before completing the study, and no patient complained of gastric discomfort; thus the upper 95% confidence limit of the incidence of this symptom with our regimen of tenoxicam was no higher than 5%.[35] The lack of a difference between groups in the incidence of nausea and vomiting is consistent with previous studies of perioperative NSAID.[1 13]

Safety is a different issue from the tolerability of a given regimen. A large prospective study is needed to quantify accurately the incidence of serious adverse events associated with perioperative NSAID and even then the question of risk *vs* benefit would probably remain a matter of opinion. The fact that there was no difference between groups for any adverse effect is consistent with many previous studies of perioperative NSAID,[1] but analgesic studies (including ours) are typically too small to allow comment on uncommon side effects, or on modest differences in the incidences of relatively common side effects. It should also be noted that our patients were healthy young adults, carefully selected to have no contraindications to NSAID, undergoing minor ambulatory surgery and taking the NSAID with food, for only 3 consecutive days. The value of a medication is reduced if large numbers of patients are unable to take it because of contraindications. It is of interest, therefore, that in the group of patients screened for this study, only five of 143 were excluded for this reason. Nevertheless, there have been numerous case reports of various side effects with NSAID and it is necessary to use them with care, particularly in the perioperative period.[1]

The analgesic efficacy of perioperative tenoxicam has been studied previously, in major and minor surgery.[12–27] We wanted to know not if tenoxicam was superior to placebo but if analgesia achieved by combining tenoxicam with paracetamol and codeine was superior to that of a paracetamol–codeine regimen alone. It is not clear from our data if Panadeine and tenoxicam had any synergistic effect, but it is clear that the addition of the NSAID provided better analgesia than could conveniently be achieved with a regimen of a paracetamol–codeine combination self-administered as needed, to a limit of two tablets 4-hourly, with no NSAID and that this was associated with less disturbance of sleep. We were surprised at how long tenoxicam continued to provide analgesia (table 3) or, from a different perspective, how long significant pain persisted after oral surgery.

It is possible that strict adherence to a regular regimen of paracetamol (or Panadeine) might have provided analgesia equal to or better than that achieved with the combination of Panadeine and tenoxicam. Anderson, Kanagasundarum and Woollard have recently shown a relationship between plasma paracetamol concentrations and analgesic efficacy.[36] For single-dose applications this should facilitate much better analgesia with paracetamol than has often been achieved in the past, but the pharmacokinetics of paracetamol do not readily lend themselves to maintaining plasma concentrations continuously above the required threshold for several days; increasing the dose beyond a reasonable limit may increase the risk of hepatotoxicity.[37] Further, our protocol reflects the clinical reality that most patients take simple analgesics on a self-titrated basis whatever the prescription. There is probably little difference between Panadeine (which contains only 8 mg of codeine per 500 mg of paracetamol) and pure paracetamol[38]; using more codeine on a repeated basis would probably increase the incidence of codeine-related side effects, and any analgesic gains would probably be slight.[38]

This study involved some inconvenience to the participants, and we were gratified to record that most patients felt positive about partaking in the study.

In summary, our data showed that tenoxicam provided a simple and well tolerated method of improving analgesia achievable with patient-titrated Panadeine alone, for several days after oral surgery. It was not the purpose of this study to compare the efficacy of tenoxicam with other NSAID which have been studied in a similar setting,[39] and our findings may well be true of most perioperative NSAID and for many different types of surgery; they probably also apply equally to paracetamol without codeine. It would be useful to confirm the value of other such combinations and to identify optimal regimens for particular perioperative models. Most importantly, there is a need for information from much larger studies on the incidence of serious side effects with perioperative NSAID.[1]

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References

1. Merry A, Power I. Perioperative NSAIDs: towards greater safety. *Pain Reviews* 1995; **2**: 268–291.
2. Dahl JB, Kehlet H. Non steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. *British Journal of Anaesthesia* 1991; **66**: 703–712.
3. Campbell WI. Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? *British Journal of Anaesthesia* 1990; **64**: 617–620.
4. Todd PA, Clissold SP. Tenoxicam: An update of its pharmacology and therapeutic efficacy in rheumatic disease. *Drugs* 1991; 41. 625–646.
5. Buckley MM-T, Brogden RN. Ketorolac: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential *Drugs* 1990; **39**: 86–109.
6. Power I. Muscle damage with diclofenac injections. *Anaesthesia* 1992; **47**: 451.
7. Campbell WI, Watters CH. Venous sequelae following i. v. administration of diclofenac. *British Journal of Anaesthesia* 1989, **62**: 545–547.
8. Gonzales JP, Todd PA. Tenoxicam, a preliminary review of its pharmacodynamic and pharmakokinetic properties and therapeutic efficacy. *Drugs* 1987; **34**: 289–310.
9. Merry AF, Wardall GJ, Cameron RJ, Peskett MJ, Wild CJ. Prospective, controlled, double-blind study of i.v. tenoxicam for analgesia after thoracotomy. *British Journal of Anaesthesia* 1992; **69**: 92–94.
10. Elhakim M, Nafie MIV. Tenoxicam for analgesia during caesarean section. *British Journal of Anaesthesia* 1995; **74**: 643–646.
11. Belzarena SD. Evaluation of intravenous tenoxicam for postoperative cesarian delivery pain relief. Preliminary report. *Regional Anesthesia* 1994; **19**: 408–411.
12. Liaw W-J, Day Y-J, Wang J-J, Ho S-T. Intravenous tenoxicam reduces dose and side effects of PCA morphine in patients after thoracic endoscopic sympathectomy. *Acta Anaesthesiologica Sinica* 1995; **33**: 73–77.
13. Gogus N, Gumus H, Gumus T, Kanbak O, Aksu C. Intravenous tenoxicam in post-operative pain. *European Journal of Anaesthesiology* 1996; **13**: 197.
14. Van Praet J, Vandenbroucke G, Evenepoel R, Boghaert A, De Loof T. The effect of preoperative administration of tenoxicam on the postoperative morphine consumption. *Acta Anaesthesiologica Belgica* 1993; **44**: 34–35.
15. Vandermeulen E, Van Aken H, Scholtes JL, Singelyn F, Haazen L. Intravenous administration of tenoxicam for postoperative analgesia. a double-blind, placebo-controlled multicentre study. *British Journal of Anaesthesia* 1995; 74 (Suppl. 1): 137.
16. Cheung LK, Rodrigo C. Tenoxicam for pain relief following third molar surgery. *Anesthesia and Pain Control in Dentistry* 1992; 1· 229–233.
17. Heinaro IP, Klami SH, Vaaja VU. A double-blind, parallel, tive study of the analgesic effects of tenoxicam and diclofenac sodium after third molar surgery. *Anesthesia and Pain Control in Dentistry* 1993; **2**: 217–222.
20. Knudsen KE, Brofeldt S, Mikkelsen S, Bille M, Brennum J, Dahl JB. Peritonsillar infiltration with low-dose tenoxicam after tonsillectomy. *British Journal of Anaesthesia* 1995; **75**: 286–288.
21. Belzarena SD. Anestesia regional intravenosa com associacao de lidocaina—tenoxicam em cirurgia ortopedica de membro superior. *Revista Brasileira de Anestesiologia* 1995; **45**: 89–94.
22. Elhakim M, Fathy A, Elkott M, Said MM. Intra-articular tenoxicam relieves post-arthroscopy pain. *Acta Anaesthesiologica Scandinavica* 1996; **40**: 1223–1226.
23. Mikkelsen SS, Knudsen KE, Kristensen BB, Linnemann MUS, Friis E, Dahl JB. Comparison of tenoxicam by intramuscular injection or wound infiltration for analgesia after inguinal herniorrhaphy. *Anesthesia and Analgesia* 1996; **83**: 1239–1243.
24. Cook TM, Tuckey JP, Nolan JP. Analgesia after day-case knee arthroscopy: double-blind study of intra-articular tenoxicam, intra-articular bupivacaine and placebo. *British Journal of Anaesthesia* 1997; **78**: 163–168.
25. Mendham JE, Mather SJ. Comparison of diclofenac and tenoxicam with and without fentanyl in children undergoing adenotonsillectomy or tonsillectomy. *Paediatric Anaesthesia* 1996; **6**: 467–473.
26. Windsor A, McDonald P, Mumtaz T, Millar JM. The analgesic efficacy of tenoxicam versus placebo in day case laparoscopy: a randomised parallel double-blind trial. *Anaesthesia* 1996; **51**: 1066–1069.
27. Jones NC, Pugh SC. The addition of tenoxicam to prilocaine for intravenous regional anaesthesia. *Anaesthesia* 1996; **51**: 446–448.
28. Heintz RC, Guenter TW, Evico JF, Dubach UC, Brand R, Jeunet FS. Pharmacokinetics of tenoxicam in healthy human volunteers. *European Journal of Rheumatology and Inflammation* 1984; **7**: 33–44.
29. Tenoxicam Data Sheet (tablet, suppository and injection). Auckland: Roche Products (NZ) Ltd, 1997.
30. Scaglione F, Demartini G, Dugnani S, Fraschini F. Pharmacokinetics of tenoxicam at different dosage regimes *Il Farmaco* 1993; **48**: 1321–1325.
31. Dallal GE. PC-Size: Consultant—a program for sample size determinations. *American Statistician* 1990; **44**: 243.
32. Monitoring during anaesthesia. College Policy Document P18. Melbourne: Australian and New Zealand College of Anaesthetists, 1995.
33. Lokken P, Skjelbred P. Analgesic and anti-inflammatory effects of paracetamol evaluated by bilateral oral surgery. *British Journal of Clinical Pharmacology* 1980; **10**: 253S–260S.
34. Dahl JB, Rosenberg J, Dirkes WE, Mogensen T, Kehlet H. Prevention of postoperative pain by balanced analgesia. *British Journal of Anaesthesia* 1990; **64**: 518–520.
35. Hanley JA, Lippmann-Hand A. If nothing goes wrong is everything all right? Interpreting zero numerators. *Journal of the American Medical Association* 1983; **249**: 1743–1745.
36. Anderson B, Kanagasundarum S, Woollard G. Analgesic efficacy of paracetamol in children using tonsillectomy as a pain

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Metabolism of remifentanil during liver transplantation

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Summary

We have investigated the pharmacokinetics of remifentanil and its less potent metabolite, GR90291, in six adult patients undergoing orthotopic liver transplantation (OLT). A single bolus infusion of remifentanil 10 µg kg^{-1} min^{-1} was given at the beginning of the dissection and anhepatic phases of OLT. Remifentanil and GR90291 concentrations were measured in subsequent serial arterial and mixed venous blood samples. Mean arterial clearance of remifentanil was significantly greater (P=0.02) in the dissection phase (79.54 ml min^{-1} kg^{-1}) than in the anhepatic phase (39.57 ml min^{-1} kg^{-1}). Steady state volumes of distribution were not significantly different. Clearance of remifentanil during the anhepatic phase was similar to that of healthy adult patients. Mean maximum concentration ($C_P$max) of GR90291 was lower in the dissection phase than in the anhepatic phase (P=0.026). There was no significant pulmonary metabolism of remifentanil. (*Br. J. Anaesth.* 1998; **81**: 881–886)

Keywords: liver, transplantation; lung, metabolism; pharmacokinetics, remifentanil, analgesics opioid, remifentanil

The demand for shorter acting, potent analgesic drugs led to the development of the phenylpiperidine group of opioids, such as fentanyl, alfentanil and sufentanil. These drugs are dependent on hepatic and renal function for their elimination and therefore accumulation and prolonged action are potential problems in the presence of significant hepatic or renal dysfunction.

Remifentanil, a new and potent phenylpiperidine opioid, is the hydrochloride salt of 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine] propanoic acid ($C_{20}H_{28}N_2O\cdot HCL$). Unlike the other members of this group, it has an ester linkage which renders it susceptible to ester hydrolysis by blood and tissue esterases. This gives it an "ultra-short" duration of action and makes its elimination independent of hepatic or renal function. The principle route of metabolism is by ester hydrolysis to a carboxylic acid metabolite, GR90291, which is excreted by the kidneys. The mean half-life of GR90291 is 88–134 min in humans[1] but it has only 1/4600 the potency of the parent compound in animal models. These properties may reduce the risks of unwanted effects, such as postoperative ventilatory depression, and accumulation of the drug in patients with hepatic or renal disease may also be less. Remifentanil is also metabolized by N-dealkylation to GI94219 but this is not a significant metabolic pathway in humans and therefore plasma concentrations of this metabolite were not measured in this study.[1]

The liver is the major organ of drug metabolism, and OLT provides a unique opportunity to determine if a drug is metabolized in other sites. Liver transplantation can be divided into three phases: the dissection phase (from the start of surgery to clamping of the hepatic blood supply and venous drainage); anhepatic phase (from clamping of the vascular supply to release of the portal vein clamp) and the reperfusion phase (which starts when the portal vein is unclamped). It is during the anhepatic phase that extrahepatic metabolism may be studied. We have used this model before to determine if there is any extrahepatic metabolism of midazolam, dopexamine or propofol.[2–4] Others have used it to study the metabolism of cyclosporin.[5]

In this study, we have compared the pharmacokinetic profiles of remifentanil after a single bolus infusion dose during the dissection and anhepatic phases of liver transplantation to investigate extrahepatic metabolism and to determine if the drug is metabolized or sequestered in the lungs.

Patients and methods

After obtaining approval from the Local Ethics Committee and informed consent, we conducted an open label, single dose, pharmacokinetic study in six patients undergoing OLT. Patients were aged 18–60 yr and were free from clinically significant cardiac, renal, pulmonary, neurological or psychiatric disease. All females were postmenopausal. Subjects were excluded if there was a positive test for hepatitis B or C; if they were 25% outside their ideal weight; if they were ASA V; and if there was a personal or family history of pseudocholinesterase deficiency or adverse reactions to opioids. Patients who had received an anaesthetic or any parenteral opioid in the previous week or had participated in a study in the preceding 4 months were also excluded. In all patients the Pugh score[6] was calculated. This is a widely used score which classifies patients with liver disease into risk groups for surgery.

All patients were anaesthetized and monitored

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according to the normal practice of our institution.[6] Four patients received temazepam 20 mg alone for premedication, one received temazepam 20 mg and ranitidine 150 mg and one received diazepam 5 mg. Anaesthesia was induced in four patients with thiopental (thiopentone) and midazolam and in the remaining two patients with thiopental alone. Four patients were given atracurium and two pancuronium for neuromuscular block and all underwent mechanical ventilation using an air–oxygen–isoflurane mixture except for one patient who received trichloroethylene instead of isoflurane. Fentanyl was used for intraoperative analgesia in all patients. We chose to measure the volume of fluids given as replacement as a better estimate of blood loss. This is because measurement of blood loss by weighing of swabs and measurement of suction losses is inaccurate.

To avoid interference with patient monitoring, a separate radial arterial cannula was used for blood sampling. After surgery patients were admitted to the intensive care unit and normal treatment continued. At the beginning of the dissection and anhepatic phases of the operation, patients were given a peripheral i.v. infusion of remifentanil 10 μg kg^{-1} over 1 min. Samples of arterial blood (6 ml) were collected in both phases for measurement of remifentanil and GR90291 concentrations. Blood was sampled before the dose of remifentanil, at the end of infusion (1 min) and at 3, 5, 7, 10, 15, 20, 25, 30, 40, 50 and 60 min thereafter. Samples of mixed venous blood (6 ml) were also collected before dosing and at 3, 5, 10, 20 and 30 min after infusion. These samples were obtained from the pulmonary artery via the pulmonary artery catheter, the position of which was confirmed by pressure measurements and waveform analysis.

In vitro hydrolysis of remifentanil in whole blood was assessed from a 30-ml sample obtained from each patient immediately before surgery. Remifentanil 2 μg was added to 20 ml of blood maintained at 37 °C. Aliquots (1 ml) were removed at 0.5, 1, 2, 4, 6, 8, 16 and 24 h to assay remifentanil concentration. The first-order decay constant was estimated by log-linear regression.

ASSAY METHODS

In order to prevent continued metabolic degradation of remifentanil after sample collection, special processing was necessary. The process consisted of immediate arrest of esterase activity in the blood sample by adding acetonitrile. Remifentanil was then extracted by adding methylene chloride to the blood–acetonitrile mixture. The organic phase was then separated and stored at −70 °C until the time of assay.

Samples were analysed for remifentanil and GR90291 using validated gas chromatographic mass spectrometry assay methods.[7 8] The lower limits of quantification for remifentanil and GR90291 were 0.1 and 0.5 ng ml^{-1}, respectively. Inter-assay coefficients of variation for remifentanil and GR90291 were ≤9.3% or ≤6.4%, respectively.

PHARMACOKINETIC ANALYSIS

Radial arterial blood concentration–time data obtained after a 1-min i.v. infusion of remifentanil during the dissection and anhepatic phases of liver transplantation were analysed by both compartmental (model-dependent) and non-compartmental (model-independent) methods. Compartmental data analysis involved fitting the blood concentration–time data for each phase to a two-compartment model with a zero-order input rate using the non-linear least squares regression analysis program PCNONLIN.[9] A weighting scheme of $1/C^2$ predicted was used. The adequacy of the model selection for further data analysis was based on the following criteria: (a) visual inspection of the residual plots, (b) magnitude of the standard error of the parameter estimates and (c) Akaike's information criteria.[10] Total body clearance (*Cl*art), steady state volume of distribution (V^{ss},art), volume of distribution of the central compartment (V_1), inter-compartment rate constants (K_{12} and K_{21}), elimination rate constant (K_{10}) and the distribution and elimination half-lives ($T_{1/2}\lambda_1$ and $T_{1/2}\lambda_2$) were estimated.

Peak remifentanil concentration ($C_p$max) was the highest observed concentration, and time to peak concentration (tC_pmax) was the time at which $C_p$max occurred. Total body clearance (*Cl*art; litre min^{-1}) was determined by dividing the total administered dose by the area under the blood remifentanil concentration–time curve (AUC) from time zero to infinity. AUC to the last sampling time (*t*last) was calculated according to the linear trapezoidal rule and the extrapolated area by dividing the value for the last concentration ($C_p$last) by the terminal rate constant (λz) of the concentration–time curve (0.006). The terminal rate constant was obtained from the compartmental analysis. The area under the first moment curve (AUMC) was estimated by the linear time–product trapezoidal rule, extrapolated to infinity by $t\text{last} \times C_p\text{last}/\lambda z + C_p\text{last}/\lambda z^2$. The mean residence time after i.v. infusion (MRTinf) was calculated by dividing AUMC by AUC. Mean residence time (MRT) was determined by subtracting the mean infusion time from the MRTinf value. For a zero-order infusion, the mean infusion time is half of the total infusion time (i.e. 1 min/2=0.5 min for this study). The steady state volume of distribution (V^{ss}, art) was determined as the product of *Cl*art and MRT.

Model-dependent arterial parameter estimates (*Cl*art, V_1 and V^{ss}, art) for both phases were compared using a paired *t* test (SAS PROC TTEST). Similarly, model-independent venous parameters (*Cl*ven and V^{ss},ven) for both phases were compared. *P* values are presented in the text.

Lung extraction ratio (ERlung) was calculated from arterial ($C_p$art) and venous ($C_p$ven) remifentanil concentrations at fixed times in each phase: ERlung=($C_p$art–$C_p$ven)/$C_p$art.

Model-independent measurements of arterial GR90291 were made, but no analysis of venous GR90291 could be performed as venous samples were collected for only 30 min. Model-dependent parameter estimates of arterial remifentanil (*Cl*art, V_1, art and V^{ss}, art) for both phases were compared using a paired *t* test (SAS V6.08).[11] Model-independent parameter estimates of arterial GR90291 for both phases were compared using an unpaired *t* test.

Results

A summary of the diagnoses, patient characteristics, normal therapy on inclusion and surgical status of the patients is shown in table 1. Time from administration of the first dose of remifentanil (during the dissection phase) to administration of the second dose (during the anhepatic phase) was 2–4 h. There was no residual remifentanil concentration at the time the second dose was administered; however, mean residual GR90291 at the time of the second dose was 4.42 (SD 3.04) ng ml^{-1} (range 0.72–8.46 ng ml^{-1}). The blood remifentanil concentration–time profiles of the six patients during both phases were characterized by a two-compartment model. Figure 1 shows the blood remifentanil concentration *vs* time profile of patient No. 1 and the theoretical curve generated from the PCNONLIN-estimated parameters.

Individual pharmacokinetic variables of arterial remifentanil are presented in table 2. These describe remifentanil as a drug with a rapid distribution phase (mean $T_{1/2}\lambda_1$ for the dissection phase, 2.32 min and mean $T_{1/2}\lambda_1$ for the anhepatic phase, 2.39 min), followed by a rapid elimination phase (mean $T_{1/2}\lambda_2$ for the dissection phase, 10.49 min and mean $T_{1/2}\lambda_2$ for the anhepatic phase, 9.96 min). The mean distribution and elimination half-lives were similar in both phases and consistent with expected values. Although there was a trend towards a greater volume of distribution (V_1) and steady state volume of distribution (V^{ss}) in the dissection phase than in the anhepatic phase, there was no significant difference between the two phases. Clearance of remifentanil, however, was significantly greater ($P=0.02$) in the dissection phase (79.54 ml min^{-1} kg^{-1}) than in the anhepatic phase (39.57 ml min^{-1} kg^{-1}).

Mean maximum concentrations ($C_p$max) of arterial GR90291 were significantly lower ($P=0.026$) in the dissection phase than in the anhepatic phase (table 3) despite the greater clearance of remifentanil in the dissection phase. We assumed a 2-h terminal elimination half-life for GR90291[1] as it is eliminated largely unchanged in the urine and is therefore independent of hepatic function.

The AUC (corrected) for the anhepatic phase was approximately twice the mean AUC for the dissection phase, a finding similar to that for the remifentanil AUC data.

Individual and mean values for the extraction ratios of remifentanil by the lung are shown in table 4 and were similar in both phases of the operation.

The mean *in vitro* half-life of remifentanil was 1.8 h. There was no significant relationship ($P>0.05$) between *in vitro* hydrolysis rate of remifentanil and anhepatic arterial clearance. Fluid losses and replacement differed between the dissection and anhepatic phases (tables 5 and 6). Significantly more fluid was given to patients during the dissection phase ($P<0.02$).

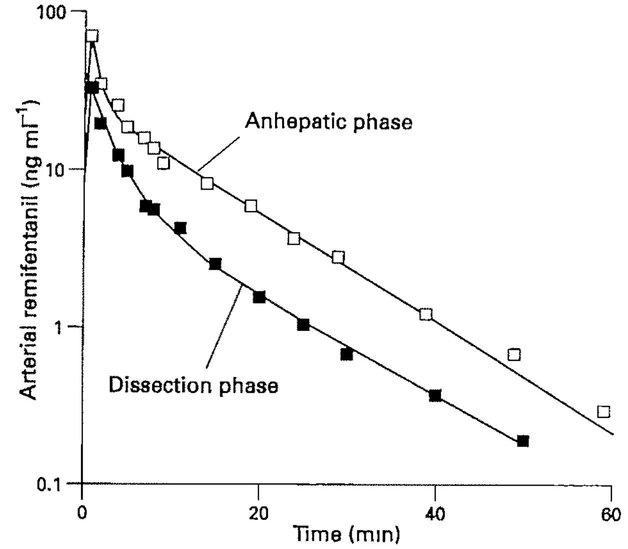

Figure 1 Arterial blood concentration–time profile of remifentanil for patient No. 1 during the hepatic and anhepatic phases. The symbols are actual data and the solid line is the predicted line.

No pharmacokinetic analysis of GR90291 in venous samples was possible because the limited sampling time did not permit a meaningful characterization of the pharmacokinetics of this compound in venous blood.

Discussion

In this study we have evaluated the pharmacokinetics of remifentanil in the presence and absence of a liver. Model-dependent and model-independent analyses were possible and conducted for remifentanil. Clearance was determined by model-independent methods and was essentially the same as that determined from the model-dependent analysis. A model-dependent analysis for GR90291 would need knowledge of the exact fraction of remifentanil metabolized by this pathway in each patient and a more complete characterization of the elimination phase of this metabolite. The pharmacokinetics of remifentanil during the dissection phase, when blood

Table 1 Patient characteristics for the six patients given remifentanil during liver transplantation

Patient No.	Sex	Age (yr)	Diagnosis	Pugh score	ASA status	Prothrombin time (s)	Usual drug therapy
1	M	43	Sclerosing cholangitis	10	III	22	Ursodeoxycholic acid, propanolol
2	F	59	Primary biliary cirrhosis	8	III	14	Propanolol, cimetidine, phenobarbital, ursodeoxycholic acid, Prempac
3	F	55	Primary sclerosing cholangitis	10	III	19.5	Ursodeoxycholic acid, ciprofloxacin, demeclocycline
4	M	47	Cryptogenic cirrhosis	12	III	22	Omeprazole, iron sulphate, spironolactone, allopurinol, lactulose
5	F	41	Primary biliary cirrhosis	8	III	16	Ursodeoxycholic acid, iron sulphate, spironolactone, Prempac, chlorpheniramine, temazepam
6	M	31	Hepatic carcinoma	5	III	12 8	Nil

Table 2 Individual arterial pharmacokinetic parameters of remifentanil during the hepatic and anhepatic phases. Total body clearance (*Cl*art), steady state volume of distribution (V^{ss}, art), volume of distribution of the central compartment (V_1), inter-compartment rate constants (K_{12} and K_{21}), elimination rate constant (K_{10}) and the distribution and elimination half-lives ($T_{\frac{1}{2}}\lambda_2$, $T_{\frac{1}{2}}\lambda_2$) and area under the curve are shown. 1/F^2 = 1/C^2 predicted

Parameter	Patient No. 1	2	3	4	5	6	Mean	SD	CV%	Median	Harmonic mean
Dissection phase											
Body wt. (kg)	72.5	54.8	55.1	88.2	43.8	85.7	66.68	18.21	27	63.80	—
Dose (μg min^{-1})	725	548	551	882	438	857	667	182.1	27	638	—
K_{10} (litre min^{-1})	0.21	0.16	0 24	0.17	0.12	0.41	0.22	0.10	47	0.19	—
K_{12} (litre min^{-1})	0.11	0.01	0.22	0.05	0.05	0.35	0.13	0.13	98	0 08	—
K_{21} (litre min^{-1})	0.13	0.06	0.22	0.14	0.06	0.21	0.14	0.07	51	0.14	—
$T_{\frac{1}{2}}\lambda_1$ (min)	1.82	3.94	1.16	2.56	3.64	0.80	2.32	1.29	56	2.19	1.68
$T_{\frac{1}{2}}\lambda_2$ (min)	9.67	13.09	7.69	7.80	17.53	7.13	10.49	4.08	39	8.74	9.44
AUC (ng min ml^{-1})	164.61	103.90	84.28	205.10	99.30	191.10	141.38	51.98	37	134.26	—
V_1, art (ml kg^{-1})	289	610	476	291	863	129	443	265	60	384	—
V^{ss}, art (ml kg^{-1})	538	736	967	388	1512	347	748	440	59	637	—
*Cl*art (ml min^{-1} kg^{-1})	60.7	96.2	118.7	48.8	100.7	52.3	79.54	29.34	37	78.43	—
R	0.992	0.994	0.999	0.997	0.979	0.999	0.993	—	—	0.996	—
Weighting factor	1/F^2	1/F^2	1/F^2	1/F^2	1/F^2	1/F^2	—	—	—	—	—
Anhepatic phase											
K_{10} (litre min^{-1})	0.25	0.12	0.14	0.19	0.21	0.11	0.17	0 06	33	0.17	—
K_{12} (litre min^{-1})	0.6	0.03	0.05	0.07	0.34	0.03	0.19	0.23	126	0.06	—
K_{21} (litre min^{-1})	0.36	0.09	0.14	0.09	0.32	0.1	0.18	0.12	67	0.12	—
$T_{\frac{1}{2}}\lambda_1$ (min)	0.61	3.66	2.74	2.39	0.89	4.06	2.39	1.41	59	2.57	1.48
$T_{\frac{1}{2}}\lambda_2$ (min)	8.63	11.5	9.04	11.4	8.15	11	9.96	1.51	15	10.04	9 76
AUC (ng min^{-1} ml^{-1})	389.7	252.1	212.9	467.9	143.6	293.5	293.28	118.62	40	272.80	—
V_1, art (ml kg^{-1})	101	321	339	111	336	318	255	115	45	319	—
V^{ss}, art (ml kg^{-1})	271	440	463	193	691	401	410	173	42	421	—
*Cl*art (ml min^{-1} kg^{-1})	25.7	39.6	47	21.4	69.6	34.1	39.57	17.39	44	36.84	—
R	0.996	0.997	1.000	0.991	1.000	0.999	0.997	—	—	0.998	—
Weighting factor	1/F	1/F^2	1/F^2	1/F^2	1/F^2	1/F^2	—	—	—	—	—

Table 3 Individual arterial pharmacokinetic parameters of GR90291 during the dissection and anhepatic phases. Time to maximum remifentanil concentration (tC_pmax), maximum concentration ($C_p$max), area under the curve (AUC),. Remifentanil concentration value for the last concentration ($C_p$last) and remifentanil concentration at the beginning of the anhepatic phase (C_{p_0}) at different times are shown. [a]AUCresidual = Co/lz; [b]AUCcorrected = AUCtotal–AUCresidual. *Significant (P=0.026)

Parameters	Patient No. 1	2	3	4	5	6	Mean	SD	CV%	Median
tC_pmax (min)	30.00	24.00	25.00	40.00	25.00	25.00	28.17	6.18	22	25.00
$C_p$max (ng ml^{-1})	13.40	12.60	18.10	19.00	16.90	12.10	15.35*	3.01	20	15.15
AUClast (ng min ml^{-1})	641	566	827	808	802	584	705	120.9	17	722
$C_p$last (ng ml^{-1})	10 9	9.31	14.0	11.4	13.8	9.06	11.4	2.13	19	11.2
AUCt-inf (ng min ml^{-1})	1887	1612	2424	1974	2390	1569	1976	368.2	19	1931
AUCtotal (ng min ml^{-1})	2529	2178	3251	2782	3192	2153	2681	480.0	18	2655
Anhepatic Phase										
Tmax (min)	39	51	40	30	30	25	35.83	9.41	26	34.50
Cmax (ng ml^{-1})	22.10	16.40	26.40	45.00	33.00	19.30	27.03*	10.55	39	24.25
AUClast (ng min ml^{-1})	1006	776	855	2286	749	916	1098	589.4	54	886
Clast (ng ml^{-1})	16.8	14.0	26.4	42.0	33.3	17.1	24.9	11.0	44	21.8
AUCt-inf (ng min ml^{-1})	2909	2424	4571	7273	5766	2961	4317	1913	44	3766
AUCtotal (ng min ml^{-1})	3915	3200	5427	9559	6516	3877	5415	2362	44	4671
C_{p_0} C_0 (ng ml^{-1})	0.716	2 88	7.09	5.35	8.46	2.00	4.42	3.04	69	4.12
AUCresidual (ng min ml^{-1})[a]	124	499	1228	926	1465	346	765	527	69	713
AUCcorrected (ng min ml^{-1})[b]	3791	2701	4199	8632	5051	3531	4651	2098	45	3995

loss, fluid replacement and haemodilution occur, were difficult to interpret. The apparent increased clearance reflected the reduced arterial concentration during this phase. The lower blood concentrations were in turn attributed to loss of remifentanil as a result of haemorrhage and the effects of haemodilution. This explanation is supported by the lower metabolite concentrations during the dissection phase. Indeed, these factors apply during the anhepatic phase but to a lesser extent. However, the presence of metabolite and the pharmacokinetic variables measured during the anhepatic phase showed that there was significant extrahepatic metabolism of remifentanil.

One of the advantages of remifentanil is its rapid blood-brain equilibration $T_{1/2}$ and associated rapid onset of action. Glass and colleagues[12] described a blood:brain equilibration half-life of 1.3 min for remifentanil. The rapid distribution and elimination half-lives of remifentanil are associated with a rapid offset of action (by virtue of a very short context-sensitive half-time[12]). This rapid onset and offset of effect may allow fine control of analgesia with remifentanil. Westmoreland and colleagues[1] and Hermann and

Table 4 Individual and mean lung uptake of remifentanil after a single bolus infusion dose of remifentanil during the dissection and anhepatic phases of liver transplantation. The arterial and venous concentrations are shown ($C_p$art and $C_p$ven respectively) together with the extraction ratio (ER). ERlung (lung extraction ratio) = ($C_p$art - $C_p$ven)/$C_p$art

		Dissection phase				Anhepatic phase		
		Remifentanil (ng/ml)				Remifentanil (ng/ml)		
Patient No.	Sampling time (min)	Arterial ($C_p$art)	Venous ($C_p$ven)	ER	Sampling time (min)	Arterial ($C_p$art)	Venous ($C_p$ven)	ER
1	2	19.29	19.1	0.01	2	34.71	33.4	0 04
2	7	4.32	6.22	–0.44	7	19.69	14.97	0.24
3	3	7.13	7.53	–0.06	3	18.49	16.73	0.11
4	3	22.3	19.04	0.15	3	42.58	45.53	–0.07
5	3	6.88	7.22	–0.05	3	11.1	10 8	0 03
6	3	14.99	16.51	–0.01	3	22.34	18.03	0 19
Mean	—	12.49	12.60	–0.07	—	24.82	23 24	0.09
SD	—	7.43	6.23	0.20	—	11.61	13.36	0.11

Table 5 Fluids administered to six patients during the dissection and anhepatic phases of liver transplantation. Significant ($P<0.02$)

	Patient No.						
	1	2	3	4	5	6	Mean (SD)
Dissection phase (litre)	1.03	6.05	4.15	5.53	2.95	3.10	3.80* (1.8)
Anhepatic phase (litre)	2.25	1.48	nil	0.80	0.20	1.10	0.97* (0.8)

Table 6 Fluid losses in six patients during the dissection and anhepatic phases of liver transplantation

	Patient No.						
	1	2	3	4	5	6	Mean (SD)
Dissection phase (litre)	4.63	2.19	0.40	2.65	0.87	1.31	2.01 (1.53)
Anhepatic phase (litre)	1.96	1.56	1.87	3.71	1.76	2.25	2.19 (0.78)

colleagues[13] described short terminal half-lives of 10–21 min and 8.8±0.98 min, respectively, which are in keeping with the half-lives described in this study. Hermann and colleagues[13] also showed that the terminal elimination half-life of alfentanil was far greater (60.9±11.6 min).

The properties suggested by such pharmacokinetic values have been supported by clinical evidence. Monk and colleagues[14] showed significantly faster recovery characteristics (time to tracheal extubation and to follow commands and discharge from the recovery area) with remifentanil compared with alfentanil in patients undergoing radical prostatectomy. This finding was confirmed by Glass and colleagues[15] who also showed remifentanil to have an analgesic potency approximately 30 times greater than alfentanil.

The pharmacokinetic and pharmacodynamic properties of remifentanil make it a potentially useful drug with distinct advantages over other phenylpiperidines when used as a single bolus dose or as an infusion. One of the main advantages is its theoretical independence from hepatic and renal metabolism. When these organs fail to function normally, accumulation of sedative and analgesic drugs (some of which have active metabolites) can delay recovery from anaesthesia and illness. In this study we compared clearance of remifentanil in the presence and absence of a liver and found it to be significantly higher during the dissection phase. However, despite the greater clearance in the dissection phase, $C_p$max values of GR90291 were less than in the anhepatic phase, although the AUC ratio for both phases was similar. If the liver were to play a role in the elimination of remifentanil, metabolite concentrations would be lower in the anhepatic phase. This was not observed. A possible explanation for the lower concentrations of GR90291 in the dissection phase is the greater blood loss and administration of larger quantities of fluid (see tables 5 and 6). This would have had a dilutional effect on both the drug and its metabolite. In future studies of this type, a control period before the dissection phase may yield useful information on drug kinetics in the absence of blood–fluid loss or haemodilution.

Mean venous clearance values for the dissection and anhepatic phases were similar to those of arterial clearance, which suggests little or almost no pulmonary clearance of remifentanil. Uptake of remifentanil into the lung (as opposed to metabolism by the lung) would be detected as a positive extraction across the pulmonary circulation initially and a negative extraction across the pulmonary circulation after distribution equilibrium with this tissue was reached. No such occurrence was detected from our data. If significant uptake were occurring, this should be detectable from the transpulmonary extraction ratio. The absence of pulmonary clearance has been confirmed by transpulmonary sampling of steady state remifentanil concentrations in coronary artery bypass graft procedure, before starting cardiopulmonary bypass.[16,17]

The *in vitro* half-life of remifentanil was significantly longer than the *in vivo* half-life, which suggests that the majority of remifentanil hydrolysis does not occur in the blood, but in the tissues, although it is uncertain if there are specific tissues in this group of patients which are responsible.

In summary, we have confirmed that remifentanil was metabolized by extrahepatic enzymes. Furthermore, it had a rapid distribution and elimination half-life in patients undergoing orthotopic liver transplantation with values that were consistent with those found in healthy volunteers. Additionally, most of the hydrolysis of remifentanil probably occurred in the extravascular compartment but the lungs did not seem to play an important role in this process.

References

1. Westmoreland CL, Hoke JF, Sebel PS, Hug CC jr, Muir KT. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GR 90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 1993; **79**: 893–903.
2. Park GR, Manara AR, Dawling S. Extrahepatic metabolism of midazolam. *British Journal of Clinical Pharmacology* 1989; **27**: 634–637.
3. Gray P, Park GR. Plasma concentrations of dopexamine during the anhepatic period of liver transplantation. *British Journal of Clinical Pharmacology* 1994; **37**: 89–92.
4. Gray P, Park GR, Cockshott ID, Douglas ED, Shuker B, Simons PJ. Propofol metabolism in human during the anhepatic and reperfusion phases of liver transplantation. *Xenobiotica* 1992; **22**: 105–114.
5. Kolars JC, Awni WM, Merion RM, Watkins PB. First pass metabolism of cyclosporin by the gut. *Lancet* 1991; **388**: 1488–1489.
6. Lindop MJ, Farman JV. Anaesthesia: Assessment and intraoperative management. In. Calne RY, ed. *Liver Transplantation*, 2nd Edn. London: Grune and Stratton, 1987.
7. Grosse CM, Davis IM, Arrendale RF, Jersey J. Determination of remifentanil in human blood by liquid–liquid extraction and capillary GC-HRMS-SIM using a deuterated internal standard. *Journal of Pharmacological and Biomedical Analysis* 1994; **12** : 195–203.
8 Lessard D, Comeau B, Charlebois A, Letarte L, Davis IM. Quantitation of GR90291 in human blood by high resolution gas chromatography/mass selective detection (HRGC/MSD) *Journal of Pharmacological and Biomedical Analysis* 1994; **12**: 659–665.
9. Metzler CM, Weiner DL. *PCNONLIN Users Guide Version 4. 1.* Statistical Consultants Inc., Lexington, KY, 1992
10. Yamaoka K, Nakagawa T, Uno T. Application of Akaike's information criteria (AIC) in the evaluation of linear pharmacokinetic equations. *Journal of Pharmacokinetics and Biopharmacology* 1978; **6**: 165–175.
11. SAS Institute. *SAS/STAT Software, Release 6. 08.* Cary: SAS Institute, 1990.
12. Glass PSA, Hardman D, Kamiyama Y, Quill TJ, Marton G, Donn KH, Grosse CM, Hermann D. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short acting opioid: remifentanil. *Anesthesia and Analgesia* 1993; **77**. 1031–1040.
13. Hermann DJ, Marton JP, Donn KH, Grosse CM, Hardman MD, Kamiyama Y, Glass PSA. Pharmacokinetic comparison of GI87084B, a novel ultra-short acting opioid, and alfentanil. *Anesthesiology* 1991; **75**: A370.
14. Monk TG, Batenhorst RL, Folger WH, Kirkham AJT, Lemon DJ, Martin KJ, Venker RPH. A comparison of remifentanil and alfentanil during nitrous–narcotic anesthesia. *Anesthesia and Analgesia* 1994; **78**: S293.
15. Glass PSA, Kapila A, Muir KT, Hermann DJ, Shiraishi M. A model to determine the relative potency of mu opioids: alfentanil versus remifentanil. *Anesthesiology* 1993; **79**: A378.
16. Duthie DJR, Muir KT, Baddoo HHK, Doyle AR, Stevens J, Kirkham AJ, Gupta SK, Frazer NM. Remifentanil is not metabolized by the lung. *Anesthesiology* 1995; **83**: A324.
17. Navapurkar VU, Archer S, Frazer NM, Gupta SK, Muir KT. Pharmacokinetics of remifentanil during hepatic transplantation. *Anesthesiology* 1995; **83**: A382.

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Continuous epidural infusion of ropivacaine for postoperative analgesia after major abdominal surgery: comparative study with i.v. PCA morphine

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Summary

We have compared the quality of three regimens of postoperative analgesia (continuous epidural administration of ropivacaine (Ropi. group), epidural ropivacaine and patient-controlled analgesia (PCA) with i.v. morphine (Ropi.+PCA group) and PCA morphine alone (PCA group)) during the first postoperative 24 h in a multicentre, randomized, prospective study. Postoperative analgesia was studied in 130 patients after major abdominal surgery performed under general anaesthesia. The ropivacaine groups received 20 ml of epidural bolus ropivacaine 2 mg ml^{-1} via the epidural route at the end of surgery, followed by continuous infusion of 10 ml h^{-1} for 24 h. The Ropi.+PCA group also had access to i.v. PCA morphine 1 mg, with a 5-min lockout. The PCA group received morphine as the sole postoperative pain treatment. The two ropivacaine groups had lower pain scores ($P<0.01$) than the PCA group. Morphine consumption was higher in the PCA group ($P<0.05$) than in the two ropivacaine groups. The quality of pain relief was rated as good or excellent in 79–85% of patients in the three groups. The percentage of patients without motor block increased between 4 and 24 h from 61% to 89% in the Ropi. group, and from 51% to 71% in the Ropi.+PCA group. (*Br. J. Anaesth.* 1998; **81**: 887–892).

Keywords: analgesic techniques, epidural; analgesia, patient-controlled; anaesthetic local, ropivacaine; pain, postoperative; surgery, abdominal

Continuous epidural infusion of a low concentration of local anaesthetic, alone or in combination with opioids, provides sustained profound analgesia with minimal sedation after major surgical procedures.[1 2] For example, postoperative epidural infusion of bupivacaine is more effective than parenteral opioids, especially during mobilization, and may reduce either postoperative morbidity or length of hospital stay.[3–7] However, toxic effects have been reported for epidural bupivacaine caused by excessive doses, low individual toxic thresholds or unrecognized intravascular injections.[8–10] Therefore, it is important that the analgesia regimens do not expose patients to an increased risk of toxic or less serious adverse effects.[4 11]

A safer substitute may be ropivacaine. Ropivacaine is a new, long-acting local anaesthetic chemically homologous to bupivacaine and mepivacaine.[12 13] In addition, ropivacaine is in the form of the S-enantiomer, making it the first enantiomerically pure local anaesthetic. Preclinical studies showed that ropivacaine induced less central nervous system and cardiac toxicity than bupivacaine.[14–18] The same decreased toxicity has been reported for ropivacaine given i.v. in human volunteers.[19 20] Further, ropivacaine induces less motor block than bupivacaine.[13 14 21] However, as yet few studies have evaluated the efficacy and safety of epidural ropivacaine (0.2%) on a large homogenous population after major abdominal surgery.[13]

Therefore, we have conducted a multicentre, open, randomized study comparing three postoperative analgesia regimens: continuous epidural ropivacaine (Ropi. group), patient-controlled analgesia with i.v. morphine (PCA group) and a combination of epidural ropivacaine and PCA morphine (Ropi.+PCA group) during the first 24 h after major abdominal surgery.

Patients and methods

After obtaining written informed consent and Institutional Ethics Committee approval, we studied 141 patients from seven hospitals. Inclusion criteria were: patients undergoing cystectomy, radical abdominal hysterectomy with pelvic lymphadenectomy, colon resection or rectum amputation, aged 18–75 yr, ASA I–III and weight 50–110 kg. Patients were excluded if they had contraindications to epidural analgesia or concomitant disease which would influence postoperative assessments.

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Patients were premedicated with lorazepam. Randomization code envelopes were opened by the investigator immediately before preparation for anaesthesia. After the randomization code was broken, the patient number was written on all labels pertaining to the study drug. Surgery was performed before 12:00 under general anaesthesia (thiopental (thiopentone), fentanyl, neuromuscular blocking drugs, isoflurane, and nitrous oxide in oxygen). After surgery, patients were allocated to one of the following three groups according to the randomization. Ropi. group: 20-ml bolus dose of ropivacaine 2 mg ml^{-1} (40 mg) followed by continuous infusion of 2 mg ml^{-1} at a rate of 10 ml h^{-1} (20 mg h^{-1}). The infusion rate was then reduced when excessive block occurred; PCA group: 1 mg i.v. bolus doses of morphine via a PCA device with a 5-min lockout time and no background infusion; Ropi.+PCA group: epidural ropivacaine as in the Ropi. group plus PCA morphine as in the PCA group.

The epidural catheter in the ropivacaine groups was inserted 4–5 cm (aimed cephalad) before induction of general anaesthesia using a 16–18-gauge needle at the appropriate interspace. A 3-ml test dose of 2% lidocaine (lignocaine) with epinephrine (adrenaline) was injected before surgery. In the PCA groups, a PCA device was connected (Abbott LifeCare PCA Infuser, Abbott Laboratories, North Chicago, IL, USA) and set to deliver 1-mg bolus doses of morphine with a 5-min lockout time. Morphine titration in the recovery room was via the PCA device after surgery. The amount of morphine used and number of demands were recorded. Additional 1–2 mg i.v. bolus doses of morphine were administered on request in all three groups.

Wound pain was assessed at rest and on coughing using a 100-mm visual analogue scale (VAS, 0 mm=no pain; 100 mm=worst pain imaginable) every hour from the end of surgery to 22:00 and thereafter every 2 h if the patient was awake. Spread of sensory block was determined by pinprick for loss and return of sensation, and motor block was assessed according to a modified Bromage scale (0=no motor block; 1=inability to raise extended legs; 2=inability to flex knees; 3=inability to flex ankle joints). Block assessment was performed every 2 h (except between 22:00 and 08:00) until return of normal sensation and motor function. Patients rated the quality of pain relief (excellent, good, intermediate or poor) at 22:00 on the day of surgery, at 08:00 on the following morning and 24 h after surgery. Arterial pressure, heart rate and body temperature were recorded every 2 h after surgery.

Adverse events were recorded as follows: spontaneously reported by the patient; observed by the research team or the ward personnel; and reported by the patient in response to open and active questions. Haemoglobin arterial saturation (Sp_{O_2}) less than 90% at any time during the study for 1 min was recorded as an adverse event. Hypotension and hypertension were defined as those episodes requiring specific treatment.

Statistical analysis was performed using SAS software (version 6.08; SAS Institute, Cary, NC, USA). Patient characteristics and intraoperative data were compared using Student's *t* test for continuous variables (normal distribution) and chi-square analysis for category variables. All postoperative variables (except adverse events) were compared with the stratum adjusted Wilcoxon (mid) rank sum test adjusted for centre. The Wilcoxon test was accompanied by Bonferroni's correction. No statistical analysis was performed on adverse events. Differences were considered statistically significant at $P \leq 0.05$. Results are expressed as mean (SD) or median (interquartile or range).

Results

Of the 141 patients enrolled, 130 patients were valid for analysis of efficacy data. Treatment for pain was discontinued in four patients because of adverse events: one patient (Ropi. group) had respiratory depression after 1.3 h and was reintubated; one patient (Ropi. group) had surgical complications after 2.5 h of infusion; and in two patients (Ropi.+PCA group and PCA group), haemorrhage occurred requiring further surgery. Seven patients were excluded from analysis because they did not receive any of the study drug: two patients withdrew their consent before surgery (Ropi. group and Ropi.+PCA group), three patients had technical failures with the epidural catheter (one in the Ropi. group and two in the Ropi.+PCA group), one patient had dural puncture (Ropi. group) and one patient underwent another surgical procedure (PCA group). The three groups were similar in age, height, weight and ASA status, but there were more women in the PCA group. Duration of surgery was similar between groups (table 1). The amounts of fentanyl (approximately 500 µg), blood loss (approximately 600 ml) and i.v. fluid requirements (approximately 4000 ml) during surgery were similar in the three groups.

Times to commencement of epidural infusion–connection of PCA device were similar in all groups. The dose of epidural ropivacaine was similar in the ropivacaine groups. Median total morphine consumption was 3.5 mg in the Ropi. group, 19.0 mg in the Ropi.+PCA group ($P<0.05$) and 51.2 mg in the PCA group ($P<0.05$ compared with the Ropi.+PCA group; $P<0.01$ compared with the Ropi. group). The median number of PCA demands was 21 for the Ropi.+PCA group whereas the corresponding value for the PCA group was 78 (table 2).

Pain scores at rest and during coughing were lower in the two ropivacaine groups compared with the PCA group, a finding that was more pronounced during the early part of the postoperative period (figs 1, 2). Pain scores in the ropivacaine groups were similar throughout. Median pain scores at rest over the 24-h postoperative period were 7–20 mm in the Ropi. group, 0–14 mm in the Ropi.+PCA group, and 13–

Table 1 Patient characteristics and duration of surgery (mean (SD))

	Group		
	Ropi. (*n*=38)	Ropi.+PCA (*n*=46)	PCA (*n*=46)
Age (yr)	57 (12)	59 (12)	56 (13)
Height (cm)	166 (9)	166 (8)	169 (8)
Weight (kg)	71 (12)	68 (14)	71 (12)
Sex (M/F)	15/23	19/27	30/16
ASA I/II/III	20/18/0	22/21/3	23/22/1
Duration of surgery (h)	3.7 (1.3)	3.7 (1.2)	3.6 (1.4)

Table 2 Details of postoperative analgesia over 24 h in the three groups: Ropi. group=epidural ropivacaine, Ropi+PCA group=epidural ropivacaine and i.v. PCA morphine, PCA group=i.v. PCA morphine only. Values are median (range). $^*P<0.05$ compared with Ropi. group, $^{**}P<0.05$ compared with the Ropi.+PCA group. For PCA attempts, only 44 patients in each group were recorded

	Group		
	Ropi. (*n*=38)	Ropi.+PCA (*n*=46)	PCA (*n*=46)
Epidural analgesia			
Epidural catheter insertion level	T12–L1	L1–L2	
Time from end of surgery to start of epidural infusion (min)	30 (6–104)	30 (0–72)	
Epidural ropivacaine (mg)	510 (411–531)	508 (397–522)	
I.v. analgesia			
Time from end of surgery to connection to PCA (min)		84 (24–360)	84 (18–300)
Total PCA morphine (mg)		19 (0–112)	41 (7–109)
PCA attempts (*n*)		21 (0–801)	78 (8–520)**
PCA accepted/demands		0.75 (0.14–1)	0.61 (0.12–1)**
Total i.v. morphine (mg)	4 (0–46)	19 (0–114)*	51 (8–131)**

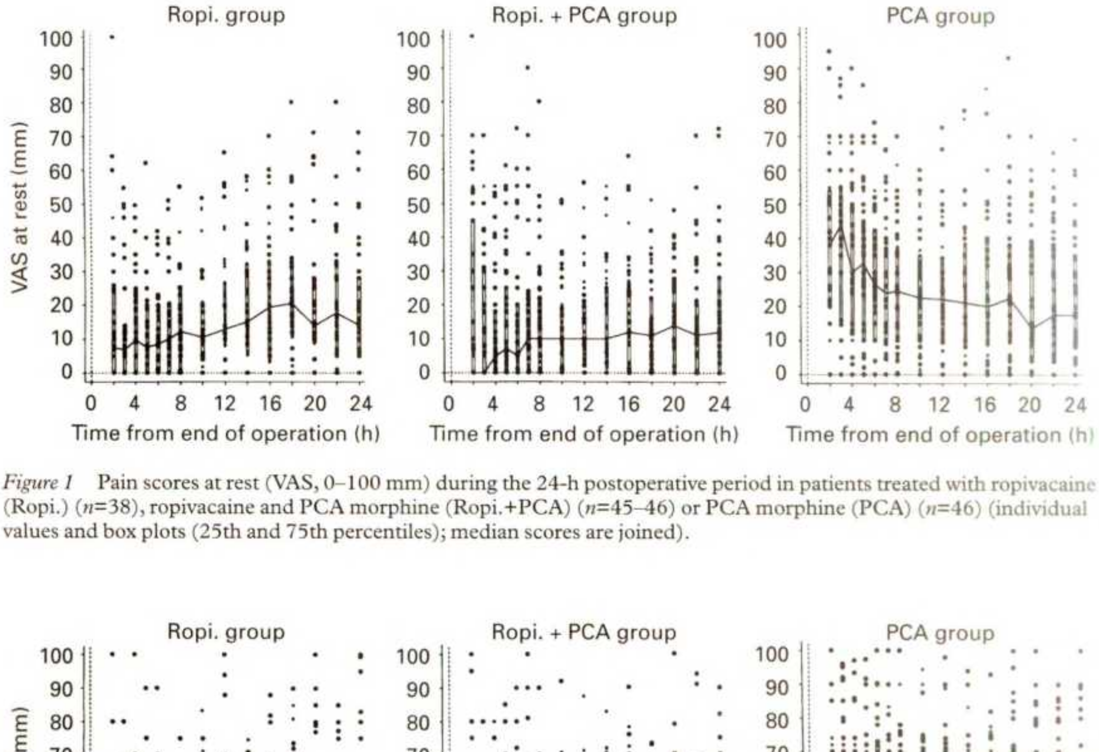

Figure 1 Pain scores at rest (VAS, 0–100 mm) during the 24-h postoperative period in patients treated with ropivacaine (Ropi.) (*n*=38), ropivacaine and PCA morphine (Ropi.+PCA) (*n*=45–46) or PCA morphine (PCA) (*n*=46) (individual values and box plots (25th and 75th percentiles); median scores are joined).

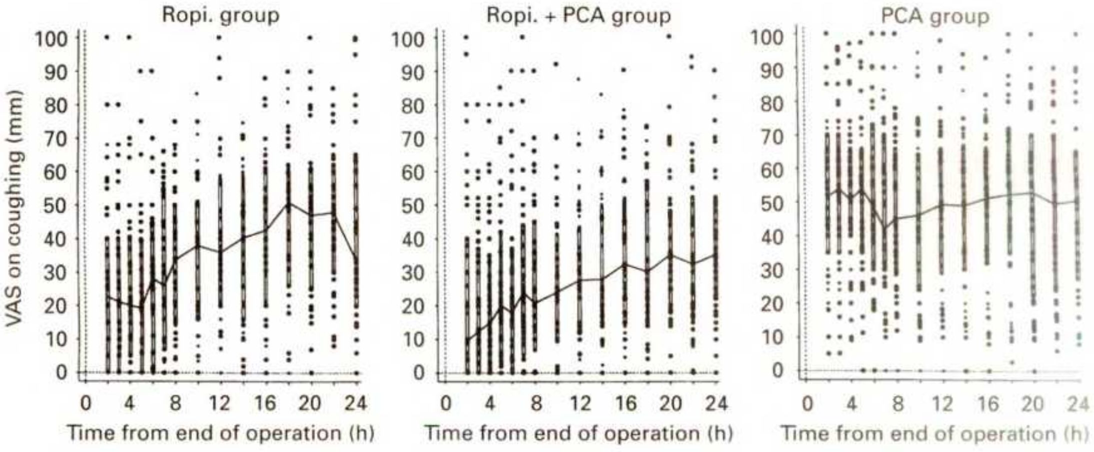

Figure 2 Pain scores during coughing (VAS, 0–100 mm) during the 24-h postoperative period in patients treated with ropivacaine (Ropi.) (*n*=38), ropivacaine and PCA morphine (Ropi.+PCA) (*n*=45–46) or PCA morphine (PCA) (*n*=46) (individual values and box plots (25th and 75th percentiles); median scores are joined).

44 mm in the PCA group. Median pain scores during coughing varied over time and were 19–51 mm in the Ropi. group, 9–35 mm in the Ropi.+PCA group and 42–54 mm in the PCA group. Comparison of the area under the curve divided by time (AUC) for VAS during coughing and at rest over 0–24 h showed a statistically significant lower AUC value for the two ropivacaine groups ($P<0.02$). There was no significant difference in AUC between the two ropivacaine groups.

The quality of pain relief assessed at 22:00 on the day of surgery was rated as good or excellent in 84% and 87% of patients in the Ropi. and Ropi.+PCA groups, respectively, compared with 64% in the PCA group ($P<0.05$). There were no significant difference between the groups at subsequent assessments.

Upper and lower spread of sensory block was similar in the two ropivacaine groups. Slight regression of the upper distribution was seen over time and was more pronounced in the Ropi. group ($P<0.05$) (fig. 3).

Motor block was less intense in patients who received ropivacaine alone than in those who received ropivacaine with PCA morphine. Sixty-one percent of patients in the Ropi. group and 51% in the Ropi.+PCA group had no demonstrable motor block 4 h after surgery. At 24 h the corresponding values were 89% and 71% (fig. 4).

The most common adverse events during the 24-h postoperative period are shown in table 3. Nausea and peripheral oxygen desaturation (<90%) were similar in all groups. Hypotension occurred more often in the Ropi.+PCA group, whereas hypertension was more common in the PCA group.

Discussion

We have demonstrated that epidural ropivacaine $2\ \mathrm{mg\ ml^{-1}}$ with or without PCA morphine provided more effective analgesia than PCA morphine alone, after major abdominal surgery. Addition of i.v. PCA morphine to epidural ropivacaine did not improve pain relief. Moreover, epidural ropivacaine reduced morphine consumption significantly compared with PCA alone. All treatment modalities were well tolerated.

Table 3 Summary of the most common adverse events during the 24-h postoperative period (number of patients). No statistical analysis was performed

	Group		
	Ropi. (n=38)	Ropi.+PCA (n=46)	PCA (n=46)
Nausea	16	17	13
Sp_{O_2} ≤90%	13	11	13
Hypotension	9	18	2
Vomiting	11	8	6
Hypertension	2	4	11

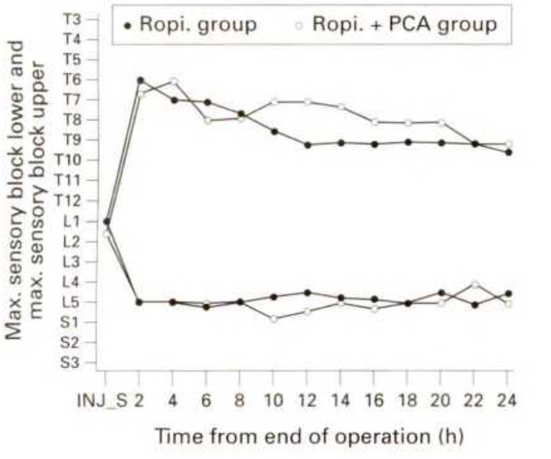

Figure 3 Upper and lower spread of sensory block during the 24-h postoperative period in patients treated with ropivacaine (Ropi.) (n=38) or ropivacaine and PCA morphine (Ropi.+PCA) (n=45–46) (median).

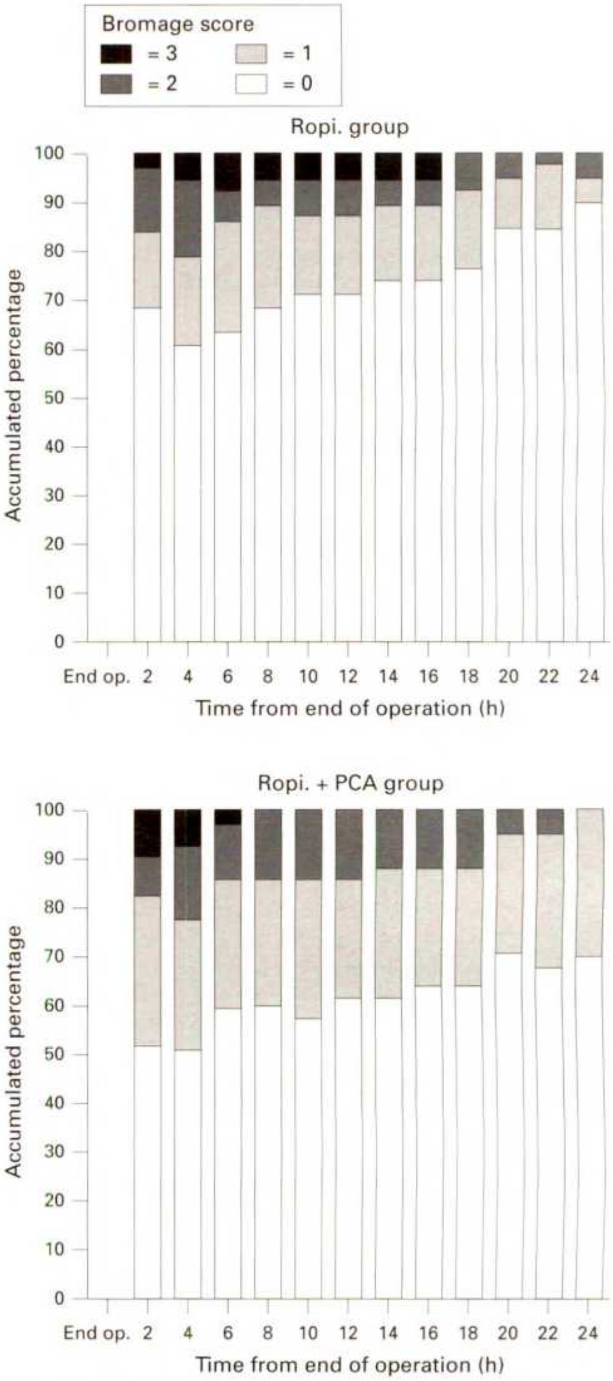

Figure 4 Motor block during the 24-h postoperative period. Modified Bromage scale (0=no motor block; 1=inability to raise extended legs; 2=inability to flex knees; 3=inability to flex ankle joints). Cumulated frequency of patients in the ropivacaine group (Ropi.) (n=38) or ropivacaine and PCA morphine group (Ropi.+PCA) (n=45–46).

With regard to pain relief, our results were comparable with other studies, and confirm that the quality of pain relief is superior with epidural analgesia using local anaesthetic compared with parenteral analgesia with opioids.[22] The combination of epidural local anaesthetics and opioids may improve pain relief and maintain sensory analgesia compared with epidural local anaesthetic alone.[22, 23] Few studies have shown that local anaesthetic alone is capable of providing efficient prolonged postoperative analgesia without causing serious adverse effects.[22] However, no synergistic effect for pain relief was demonstrated when i.v. morphine was added to epidural ropivacaine in our study, except for regression of the sensory level of analgesia. In a previous study, co-administration of epidural bupivacaine with i.v. morphine restored the sensory level of analgesia and, unlike that observed in our study, enhanced the quality of analgesia.[24]

Analgesia was not optimal in every patient in the ropivacaine groups. Suboptimal pain relief in some patients may be explained by inadequate doses of the analgesic, inadequate level of sensory block or catheter misplacement. Interestingly, patients in the Ropi.+PCA group who had easy access to supplementary morphine, consumed more opioid than those in the Ropi. group, suggesting that pain tolerance depends on environment, but the higher morphine consumption in the Ropi.+PCA group could jeopardize the rate of recovery.[3,7] However, PCA attempts were significantly less frequent in the Ropi.+PCA group than in the PCA group. Also, the delivery/demand ratio for the PCA device was higher in the Ropi.+PCA group than in the PCA group. The successful PCA attempts or the high PCA accepted/demands ratio were probably attributable to better quality of pain relief observed in the Ropi.+PCA group during the first night. It has been shown previously that the ratio between successful delivery of morphine and requests is correlated inversely with the degree of pain reported by VAS.[25] The optimal combination of local anaesthetics and opioids providing optimal analgesia and minimal complications has yet to be identified. Moreover, the use of only local anaesthetic could help to avoid opioid-induced side effects and in this study, addition of i.v. morphine did not improve pain relief. Several studies have investigated the use of continuous epidural infusions of ropivacaine as pain relief after either upper, lower or orthopaedic surgery.[26–31] Pain (either at rest or induced by coughing) becomes proportionally less severe as the dose of ropivacaine increases. Also, morphine consumption decreases as the dose of ropivacaine increases.[26–31] Scott and colleagues concluded that for postoperative analgesia, an epidural infusion of 0.2% ropivacaine provided the best balance of analgesia with minimal motor block.[27] In our study, we only evaluated the effect of a single dose of epidural ropivacaine (0.2%) on a large homogenous population after major abdominal surgery (mean duration 3.6±1.3 h).

Motor block, which is undesirable in a postoperative situation, becomes more intense as the dose of ropivacaine increases.[27,28,30,31] However, in a study using different concentrations (1, 2 and 3 mg ml^{-1}) of mid-low thoracic epidural ropivacaine after upper abdominal surgery, motor block was negligible (10% of patients with Bromage scores of 1 and 2).[26] In our study, a higher incidence of motor block was observed with regression over time. The incidence of significant motor block was similar to that of a previous study conducted under the same conditions.[28] A possible explanation for the higher intensity of motor block in the combined treatment group could be a synergistic effect on the central nervous system of ropivacaine combined with PCA morphine.[32] Studies of lumbar epidural block in humans have confirmed that equal volumes and concentrations of ropivacaine and bupivacaine produce a similar pattern of sensory block but motor block is slower in onset, less intense and shorter in duration with ropivacaine.[14,21,33] Large myelinated A fibres transmit motor impulses. The rate of block of A fibres depends on the physicochemical properties of the drugs, high pKa and low lipid solubility favouring block of C fibres over A fibres.[34] Ropivacaine is less likely to block A fibres than bupivacaine. This has been confirmed *in vitro*.[35]

The most frequently reported adverse event during the 24-h postoperative period was nausea, which occurred with a similar frequency in the three groups. Vomiting was slightly more common in patients treated with ropivacaine alone than in patients given PCA morphine. These events may have occurred because all patients received fentanyl during general anaesthesia and because the surgical procedure itself may also have contributed to the onset of these side effects. Hypotension was seen more frequently in patients given ropivacaine. The incidence of systemic hypotension in our Ropi. group (22%) was similar to that of our previous study and to that of others.[5,14,22] In contrast, hypertension was observed more often in patients receiving PCA morphine alone.

In summary, epidural ropivacaine administered as a continuous infusion of 2 mg ml^{-1} with or without i.v. PCA morphine gave superior postoperative pain relief both at rest and on coughing in patients undergoing major abdominal surgery than PCA morphine alone. The benefit/risk ratio of potent postoperative analgesia treatment has to be evaluated constantly.

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References

1. Scott DA, Bleiby DSN, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. A prospective analysis of 1014 patients. *Anesthesiology* 1995, **83** 727–737.
2. De Leon-Cassassola OA, Parker B, Lema MJ, Harrison P, Massey J. Postoperative epidural bupivacaine–morphine therapy. *Anesthesiology* 1994, **81** 368–375.
3. Liu S, Carpenter RL, Neal J Epidural anesthesia and analgesia, their role in postoperative outcome. *Anesthesiology* 1995; **82**. 1474–1506
4. Wheatley RG, Madej TH, Jackson IJB, Hunter D. The first year's experience of an acute pain service. *British Journal of Anaesthesia* 1991; **67**: 353–359.
5. Jayr C, Thomas H, Rey A, Farhat F, Lasser PH, Bourgain JL. Postoperative pulmonary complications. Epidural analgesia using bupivacaine and opioids versus parenteral opioids *Anesthesiology* 1993; **78**· 666–676.
6. Dahl JB, Rosenberg J, Hansen BL, Hjortso NC, Kehlet H Differential analgesic effects of low-dose epidural morphine and morphine–bupivacaine at rest and during mobilization after major abdominal surgery. *Anesthesia and Analgesia* 1992; **74**: 362–365
7. Thorén T, Sundberg A, Watwil M, Garvill JE, Jürgensen U. Effects of epidural bupivacaine and epidural morphine on bowel function and pain after hysterectomy *Acta Anaesthesiologica Scandinavica* 1989; **33**· 181–185.
8. Albright, GA Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979, **51**· 285–287.
9. Editorial. Cardiotoxicity of local anaesthetic drugs. *Lancet* 1986; **2**· 1182–1194.
10. Ryan DW. Accidental intravenous injection of bupivacaine. A complication of obstetrical epidural anaesthesia *British Journal of Anaesthesia* 1973, **43** 907–908.
11. Kehlet H. Postoperative pain relief—what is the issue? *British Journal of Anaesthesia* 1994; **72**: 375–378.
12. McClure JH. Ropivacaine. *British Journal of Anaesthesia* 1996; **76**: 300–307.

13. Markham A, Faulds D. Ropivacaine. A review of its pharmacology and therapeutic use in regional anesthesia. *Drugs* 1996, **52**: 429–449
14. Cederlhom I. Preliminary risk–benefit analysis of ropivacaine in labour and following surgery. *Drug Safety* 1997; **16**: 391–402.
15. Danielsson BRG, Danielson MK, Böö EL, Arvidsson T, Halldin MM. Toxicity of bupivacaine and ropivacaine in relation to free plasma concentrations in pregnant rats· a comparative study. *Pharmacology and Toxicology* 1997; **81**. 90–96.
16. Feldman HS, Arthur GR, Pitkanen M, Hurley R, Doucette AM, Covino BG. Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. *Anesthesia and Analgesia* 1991; **73**: 373–384.
17. Feldman HS, Arthur GR, Covino BG. Comparative systemic toxicity of convulsant and supraconvulsant dose of intravenous ropivacaine, bupivacaine and lidocaine in the conscious dog. *Anesthesia and Analgesia* 1989; **69**: 794–801.
18. Rutten AJ, Nancarrow C, Mather LE, Isley AH, Runciman WB, Upton RN. Hemodynamic and central nervous system effects of lidocaine, bupivacaine and ropivacaine in sheep. *Anesthesia and Analgesia* 1989; **69**: 291–299.
19. Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesthesia and Analgesia* 1989; **69**: 563–569.
20. Knudsen K, Beckman-Suurküla M, Blomberg S, Sjövall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *British Journal of Anaesthesia* 1997; **78**· 507–514.
21. Zaric D, Nydahl PA, Philipson L, Samuelsson L, Heierson A, Axelsson K The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2% and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers: a double-blind study. *Regional Anesthesia* 1996, **21**: 14–25.
22. Shafer AL, Donnely AJ. Management of postoperative pain by continuous epidural infusion of analgesics. *Clinical Pharmacology* 1991; **10**: 745–764.
23. Kaneko M, Saito Y, Krihara Y, Collins JG, Kosaka Y. Synergistic antinociceptive interaction after epidural coadministration of morphine and lidocaine in rats. *Anesthesiology* 1994; **80**: 137–150.
24. Lund C, Mogensen T, Hjortso NC, Kelhet H. Systemic morphine enhances spread of sensory analgesia during postoperative epidural bupivacaine infusion. *Lancet* 1985; **2**: 1156–1157.
25. McCoy EP, Furness G, Wright PM. Patient-controlled analgesia with and without background infusion. Analgesia assessed using the demand:delivery ratio. *Anaesthesia* 1993; **67**: 256–260.
26. Schug SA, Scott DA, Payne J, Mooney PH, Hagglöf B. Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery. *British Journal of Anaesthesia* 1996; **76**: 487–491.
27. Scott DA, Chamely D, Mooney PH, Deam RK, Mark AH, Hagglöf B. Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery. A dose finding study. *Anesthesia and Analgesia* 1995; **81**: 982–986.
28. Etches RC, Writer WDR, Ansley D, Nydahl PA, Ong BY, Lui A, Badner N, Kawolski S, Muir H, Shulka R, Beattie WS. Continuous epidural ropivacaine 0.2% for analgesia after lower abdominal surgery. *Anesthesia and Analgesia* 1997; **84**: 784–790.
29. Erichsen CJ, Svojall J, Kehlet H, Hedlund C, Arvidsson T. Pharmacokinetics and analgesic effect of ropivacaine during continuous epidural infusion for postoperative pain relief. *Anesthesiology* 1996; **84**: 834–842.
30. Badner NH, Reid D, Sullivan P, Ganapathy S, Crosby ET, McKenna J, Lui A. Continuous epidural infusion of ropivacaine for the prevention of postoperative pain after major orthopaedic surgery: a dose-finding study. *Canadian Journal of Anaesthesia* 1996; **43**: 17–22.
31. Turner G, Blake D, Buckland M, Chamley D, Dawson P, Goodchild C, Mezzatesta J, Scott D, Sultana A, Walker S, Hendrata M, Mooney P, Armstrong M. Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery. *British Journal of Anaesthesia* 1996; **76**: 606–610.
32. Åkerman B, Arweström E, Post C. Local anesthetics potentiate spinal morphine antinociception. *Anesthesia and Analgesia* 1988; **67**: 943–948.
33. Brockway MS, Bannister J, McClure JH, McKewn D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. *British Journal of Anaesthesia* 1991, **66**: 31–37.
34. Wildsmith JAW, Brown DT, Paul D, Johnson S. Structure activity relationship in differential nerve block at high and low frequency stimulation. *British Journal of Anaesthesia* 1989; **63**: 444–452.
35. Bader AM, Datta S, Flannagan H, Covino BG. Comparison of bupivacaine- and ropivacaine-induced conduction blockade in the rabbit isolated vagus nerve *Anesthesia and Analgesia* 1989; **68**: 724–727.

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Epidural analgesia with bupivacaine does not improve splanchnic tissue perfusion after aortic reconstruction surgery†

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Summary

Inadequate splanchnic tissue perfusion is relatively common during and after aortic surgery. We hypothesized that vasodilatation caused by thoracic epidural analgesia improves splanchnic blood flow and tissue perfusion after aortic surgery. In this prospective, randomized, controlled study, we studied 20 patients undergoing elective aortic-femoral or aortic-iliac reconstruction surgery. Gastric and sigmoid colon mucosal $P\text{co}_2$ and pH were measured during surgery. An epidural bolus of bupivacaine 40 mg followed by infusion of 15 mg h^{-1} was started after operation in 10 patients. After operation, splanchnic blood flow and gastric and sigmoid colon mucosal $P\text{co}_2$ and pH were measured before and 2 h after the start of epidural analgesia. During surgery, the gastric mucosal–arterial $P\text{co}_2$ difference remained stable, whereas the sigmoid mucosal–arterial $P\text{co}_2$ difference increased during aortic clamping but returned to pre-clamping values after declamping. After operation, epidural analgesia had no effect on gastric or sigmoid mucosal–arterial $P\text{co}_2$ differences or on splanchnic blood flow. (*Br. J. Anaesth.* 1998; **81**: 893–898)

Keywords: analgesic techniques, epidural; surgery, vascular; gastrointestinal tract, blood flow; anaesthetics local, bupivacaine

The incidence of bowel ischaemia diagnosed by sigmoideoscopy varies between 1.1 and 10% after reconstructive surgery of the abdominal aorta[1–3]: this is increased at least two-fold after aortic surgery for ruptured aortic aneurysm.[1] Bowel ischaemia may result from interruption of the blood supply caused by surgery, reduced systemic blood flow, regional perfusion abnormalities or a combination of these.

Gastric mucosal acidosis has been shown to be a sign of poor prognosis in critically ill patients[4] and is a predictor of poor outcome after aortic surgery for ruptured abdominal aortic aneurysm, suggesting that inadequate tissue perfusion is related to the development of organ dysfunction.[5] In aortic surgery, sigmoid colon mucosal tonometry may reveal ischaemia caused by decreased cardiac output and arterial pressure, in addition to ischaemia caused by local vascular occlusion. Several studies have shown that sigmoid mucosal acidosis in aortic surgery is associated with poor outcome.[6–8] In aortic surgery, low sigmoid mucosal pH is associated with high endotoxin concentrations and remote organ dysfunction.[9]

Prevention of gastric mucosal acidosis has been suggested to improve prognosis in critically ill patients. Peri- and postoperative supranormal systemic oxygen delivery ($D\text{o}_2$) has improved outcome in selected groups of high-risk surgical patients.[10 11] Although increased systemic $D\text{o}_2$ may improve the perfusion of the gut, interventions to increase whole body blood flow may worsen the gastric mucosal acidosis.[12 13] An attractive alternative to manipulate visceral perfusion is epidural block, which is used widely in postoperative pain management after aortic surgery. Sympathetic block after thoracic epidural anaesthesia should cause mesenteric vasodilatation and increase intestinal motility, and therefore may be beneficial for gut perfusion after aortic surgery.[14 15]

We hypothesized that epidural analgesia improves splanchnic blood flow and tissue perfusion after abdominal aortic surgery. To test this hypothesis, we measured the effect of epidural analgesia on splanchnic blood flow and tissue perfusion after operation in patients undergoing elective aortic reconstructive surgery.

Patients and methods

The study was approved by the Hospital Ethics Committee and written informed consent was obtained from each patient. Gastric and sigmoid mucosal pH was monitored in the peri- and postoperative periods in 20 patients undergoing elective abdominal aortic surgery because of aorto-iliac occlusive disease or abdominal aortic aneurysm. There were no exclusion criteria. To test the effect of epidural analgesia on splanchnic blood flow, patients were allocated randomly to one of two groups: 10 patients received postoperative epidural analgesia with bupivacaine after baseline measurement of hepatosplanchnic blood flow, and the remaining 10 patients served as controls. Clinical data of the patients are shown in table 1.

Before induction of general anaesthesia, an epidural catheter was inserted in each patient, except for one patient in the control group who received chronic anticoagulant therapy. The epidural cathether was used for postoperative analgesia in

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these 19 patients after completion of the study. The epidural catheter was inserted at the T12–L1 interspace using a standard loss of resistance technique and the catheter was inserted 5 cm inside the epidural space. A test dose of 50 mg of 1% lidocaine with epinephrine (adrenaline) 5 μg ml^{-1} was injected through the catheter. General anaesthesia was induced with fentanyl 20 μg kg^{-1} and a mixture of alcuronium 0.125 mg kg^{-1}, pancuronium 0.075 mg kg^{-1} and midazolam 0.07 mg kg^{-1}. Anaesthesia was maintained with continuous infusion of fentanyl 0.07 μg kg^{-1} min^{-1}, alcuronium 1 μg kg^{-1} min^{-1} and midazolam 0.6 μg kg^{-1} min^{-1}, and was supplemented with thiopental (thiopentone) and isoflurane. Monitoring included pulmonary artery catheterization and we aimed to maintain cardiac index >2.0 litre min^{-1} m^{-2} by infusing crystalloids, colloids and blood. None of the patients received inotropic agents. During the surgery, sodium nitroprusside was used to treat systemic hypertension when systolic arterial pressure exceeded 160 mm Hg, despite supplementation of anaesthesia with thiopental or isoflurane. After operation, sodium nitroprusside was also used to treat hypertension when systolic arterial pressure exceeded 160 mm Hg. The arterial pressure limit was defined by the surgeon in charge of the operation. One patient received nitroglycerine in the perioperative period for a short time because of ST-elevation in the ECG, but after operation there were no signs of myocardial injury and recovery was uneventful. The aorta was clamped above the renal arteries in one patient and below the renal arteries in the remaining 19 patients. Duration of aortic clamp was 94±35 min. In three patients (two in the control group and one in the epidural group) the aorta was occluded only partially. No reimplantations of the inferior mesenteric artery were performed.

TONOMETRY

To assess mucosal perfusion, both gastric mucosal $P\text{CO}_2$ and pH, and sigmoid mucosal $P\text{CO}_2$ and pH were measured in the peri- and postoperative periods by gastric and sigmoid tonometers (Tonomitor, Tonometrics, Worcester, MA, USA). Equilibration time was 30 min during aortic clamping and 60–90 min for other samples.[16] Gastric and sigmoid mucosal pH was calculated using a modification of the Henderson–Hasselbach equation. Intramucosal–arterial $P\text{CO}_2$ difference was calculated as gastric/sigmoid intramucosal $P\text{CO}_2$– arterial $P\text{CO}_2$, and arterial–intramucosal pH difference as arterial pH–gastric/sigmoid intramucosal pH. Two patients in the epidural group and one patient in the control group received a H_2 receptor antagonist at induction of anaesthesia because of a previous history of gastric ulcer. In critically ill patients, the use of H_2 receptor antagonists has not been demonstrated to influence gastric mucosal pH values or to improve the reproducibility of determination of gastric mucosal pH.[17 18] The gastric tonometer was inserted after induction of anaesthesia, and the correct position was verified by the surgeon. The sigmoid tonometer was inserted into the rectum and manipulated to the mid-sigmoid position at laparotomy. The correct position of the tonometers was confirmed again just before closure of the abdomen, and for the gastric tonometer also by chest x-ray obtained in the intensive care unit.

Systemic haemodynamic variables, arterial and mixed venous blood-gas tensions and oxygen saturation, and haemoglobin and plasma lactate concentrations were measured before induction of anaesthesia, before aortic occlusion, during aortic occlusion and at the end of surgery. Plasma lactate concentrations were measured enzymatically (Stat Plus 2300, Yellow Springs Instrument Co., OH, USA). Blood-gas tensions and $P\text{CO}_2$ from the tonometers were measured with the same blood-gas analyser (ABL 500 Blood Gas System, Radiometer A/S, Copenhagen, Denmark) and corrected for actual body temperature. Cardiac output was measured by thermodilution in triplicate using saline 10 ml at room temperature. During operation, systemic oxygen consumption ($\dot{V}\text{O}_2$) was calculated according to Fick's principle. Gastric and sigmoid mucosal $P\text{CO}_2$ and pH were measured before aortic occlusion, during occlusion (30 min after clamping the aorta) and at the end of operation.

The study was performed in the intensive care unit where the patient's lungs were ventilated using controlled mechanical ventilation (Servo 900C, Siemens AB, Solna, Sweden) with an $F\text{I}_{\text{O}_2}$ of 0.4–0.5 and a PEEP of 5 cm H_2O. Adequacy of sedation was confirmed by careful bedside monitoring and, if necessary, bolus doses of thiopental or oxycodone chloride were given. The hepatic vein was cannulated via the right internal jugular vein, and the correct position verified with fluoroscopy using a small amount of contrast dye. After baseline measurement of splanchnic blood flow, 10 patients in the epidural group received an epidural 40-mg bolus of 0.5% bupivacaine followed by an infusion of 15 mg h^{-1}. In the control patients, no epidural injection or infusion was given. In order to detect successful sympathetic block, mean arterial pressure was evaluated 50 min after the start of epidural analgesia (epidural: mean 90 (SD 12) *vs* 71 (9) mm Hg; control: 94 (15) *vs* 89 (12) mm Hg; $P<0.05$ between groups, two way analysis of variance for repeated measurements). Measurement of splanchnic blood flow was repeated 2 h after baseline measurements. During splanchnic blood flow measurement, systemic $\dot{V}\text{O}_2$ was measured continuously from the inspired and expired gases by open circuit indirect calorimetry (Deltatrac, Datex-Engström Corp., Helsinki, Finland). The device has been validated in this laboratory and it has a relative error of less than 5% under the study conditions.[19]

Splanchnic blood flow was measured using the dye dilution method, described previously.[20] In brief, after a priming dose of 12 mg of indocyanine green injected into a peripheral vein, a constant infusion of 1.1 mg min^{-1} was continued for 30 min. Blood was sampled for measurement of indocyanine green concentrations in arterial and hepatic venous blood after 20, 25 and 30 min of infusion. In order to evaluate if steady state dye concentrations were achieved, the coefficient of variation was calculated for each individual during each blood flow measurement. Indocyanine green concentrations were in steady-state plateau, as indicated by a coefficient of variation of 2.8 ± 2.1% in radial arterial blood and 4.0 ± 3.0% in hepatic venous blood. Indocyanine green extraction was 71.0 ± 10.9% (range 41–89%). Within-subject coefficient of variation for splanchnic blood flow, based on three consecutive blood samples of each measurement period, was 4.6 ± 3.6%.

STATISTICAL ANALYSIS

For sample size calculations, we assumed an SD of 0.2 litre min^{-1} m^{-2} for splanchnic blood flow and 0.068 for mucosal pH, and a within-subject coefficient of variation of 4% for splanchnic blood flow measurements based on our previous studies.[20,21] Using a two-sided α of 0.05, this would allow us to detect a change of 0.18 litre min^{-1} m^{-2} in splanchnic blood flow and 0.06 pH units in mucosal pH with 80% power with 10 evaluable patients per group.

Friedman one-way analysis of variance was used to detect changes during surgery. If statistically significant changes were found, the Wilcoxon signed ranks test was used *post hoc* to locate the changes. The tonometry data were compared with preclamping values and haemodynamic data with preoperative values. The Bonferroni correction was used for multiple comparisons. Postoperative data were tested using two-way analysis of variance for repeated measurements. The values that failed the normality test were tested using the Kruskal–Wallis non-parametric test (sigmoid–arterial $P\text{co}_2$ difference in the second blood flow measurement). Findings were considered significant if $P<0.05$. All results are presented as mean (SD), unless otherwise stated.

Results

Clinical data of the patients are presented in table 1. Three patients required intensive care for 2–4 days because of postoperative respiratory failure (two patients in the epidural and one patient in the control group) and two patients in the control group and one patient in the epidural group had postoperative wound infection.

Peri- and postoperative haemodynamic and oxygen transport data are shown in tables 2 and 3. During surgery, the gastric–arterial $P\text{co}_2$ difference and arterial–gastric pH-gap remained unchanged. In contrast, sigmoid–arterial $P\text{co}_2$ difference and arterial–sigmoid pH gap increased after aortic occlusion but returned to preclamping values by the end of surgery (fig. 1).

At baseline, in the intensive care unit, there were no differences between the epidural and control groups for haemodynamic variables, splanchnic blood flow or oxygen transport (tables 3, 4, fig. 2). Mean arterial pressure decreased in both groups after 2 h but there were no significant differences between groups (table 3). There were no differences in gastric–arterial or sigmoid–arterial $P\text{co}_2$ differences or arterial–gastric or arterial–sigmoid pH-gaps between the groups after operation (table 3).

Hepatic venous oxygen saturation decreased and hepatic venous lactate and splanchnic oxygen extraction increased, but there were no differences between the groups (table 4). Hepatic lactate uptake was higher in the epidural group.

Six patients in the epidural group and nine patients in the control group received sodium nitroprusside in the intensive care unit during splanchnic blood flow measurements and the infusion rate was maintained constant during the measurements. The need for sodium nitroprusside in the epidural group decreased during epidural analgesia (epidural: mean: 1.2 (SD 1.8) (range 0–6.0) *vs* 0.3 (0.6) (0–1.6) $\mu\text{g kg}^{-1}$ min^{-1}; control: 1.6 (1.7) (0–4.7) *vs* 2.0 (2.3) (0–7.2) $\mu\text{g kg}^{-1}$ min^{-1}).

Table 1 Clinical data of the patients (mean (SD or range) or number)

	Epidural group	Control group
Sex (M/F)	9/1	7/3
Age (yr)	65 (54–76)	61 (51–68)
Diagnosis		
Aorto-iliac occlusive disease	5	8
Abdominal aortic aneurysm	5	2
Preoperative disease		
Coronary artery disease	3	6
Myocardial infarction	2	1
Pulmonary disease	0	2
Hypertension	3	3
Preoperative medication		
Beta-blockers	5	2
Nitrates	1	4
Ca blockers or ACE inhibitors	4	3
Acetylsalicylic acid	6	5
Type of surgery		
Aorto-femoral bypass	6	9
Aorto-iliacal bypass	4	1
Duration of aortic clamp (min)	101 (36) (54–166)	87 (34) (30–141)
Inferior mesenteric artery occluded before operation	6	6
Duration of intensive care (days)	1 4 (1 0) (1–4)	1 1 (0.3) (1–2)
Duration of hospital stay (days)	10 (4) (7–17)	8 (2) (6–13)

Discussion

The main finding of the study was that epidural analgesia after abdominal aortic reconstruction surgery did not improve splanchnic tissue perfusion, as assessed by mucosal tonometer and measurements of total hepatosplanchnic blood flow. Mucosal acidosis was uncommon and mucosal perfusion or metabolism was evidently not affected by epidural analgesia.

There are few studies on the effect of epidural block on intestinal perfusion. Johansson and colleagues concluded that during colorectal surgery, epidural bupivacaine had a favourable effect on intestinal blood flow measured by laser Doppler flowmetry.[22] Sutcliffe and colleagues found that perioperative gastric mucosal acidosis was less common with epidural anaesthesia in a heterogeneous group of major surgery patients.[23] Because data on haemodynamics and volume status were not given, interpretation of this observation is difficult. Increased volume substitution because of hypotension induced by epidural anaesthesia may have prevented splanchnic hypoperfusion caused by persistent hypovolaemia.[24] Animal studies have demonstrated that the haemodynamic response is dependent on the spread of epidural block.[14,15] Hogan and colleagues [14,15] showed that hypotension after lumbar epidural anaesthesia causes splanchnic vasoconstriction because of baroreceptor activation, while thoracic epidural anaesthesia blocks sympathetic activity, resulting in mesenteric vasodilatation. Hepatic arterial blood flow did not change in response to epidural anaesthesia in their animal model. It is conceivable that in humans also, volume status and hypotension may modify the response of blood flow distribution to epidural block.

In our study, assessment of neural block was not feasible because of residual general anaesthesia.

Table 2 Systemic haemodynamic state and oxygen transport during surgery. * $P<0.05$ *vs* before induction; † $P<0.05$ *vs* before clamping (Wilcoxon) (mean (SD))

	Before induction	Before clamping	30 min after clamping	End surgery	Friedman one-way ANOVA *P* value
CI (litre min^{-1} m^{-2})	2.9 (0.61)	2.3 (0.61)*	2.0 (0.32)*	2.6 (0.38)	0.0000
MAP (mm Hg)	86 (15)	73 (11)*	75 (8)*	83 (11)	0.0021
PCWP (mm Hg)	12 (4)	9 (4)	9 (3)	10 (2)	0.3333
$\dot{V}o_2$ Fick (ml min^{-1} m^{-2})	133 (29)	96 (24)*	83 (25)*	91 (12)*	0.0000
O_2 extraction	0.27 (0.04)	0.28 (0.06)	0 29 (0.08)	0.24 (0.06)	0 0072
Core temperature (°C)	36.5 (0.3)	35.5 (0.4)*	35.5 (0.5)*	35.3 (0.8)*	0.0000
Gastric–arterial $P\text{CO}_2$ difference (kPa)		1.30 (0.65)	1.48 (1.76)	1.08 (0.69)	0.0351
Sigmoid–arterial $P\text{CO}_2$ difference (kPa)		2.67 (2.00)	5.22 (3.74)†	2.38 (2.22)	0.0004
Arterial–gastric pH-gap		0.09 (0.06)	0.09 (0.10)	0.07 (0.05)	0.1653
Arterial–sigmoid pH-gap		0.20 (0.12)	0 31 (0.17)†	0.16 (0.10)†	0.0003

However, the acute reduction in mean arterial pressure in the epidural group and the reduced need for sodium nitroprusside suggests successful sympathetic block. The dose of bupivacaine used in our study was likely to produce and maintain at least partial thoracic sympathetic block.[25] Nydahl and colleagues have shown that cephalad spread of epidural anaesthesia is more extensive in elderly patients than in the young.[26] In their study, 0.5% bupivacaine 20 ml injected at L2–3 into the epidural space caused analgesia to pinprick at and below T4. Recently, Visser and co-workers showed that low thoracic epidural block with lidocaine 60 mg injected at T7–9 spread 7.7 ± 1.8 segments upwards.[27] We cannot exclude the possibility that sympathetic block up to T5 was not achieved. Nevertheless, most of the local anaesthetic should have spread into the area of the coeliac and superior and inferior mesenteric ganglions. Accordingly, insufficient sympathetic block is unlikely to explain the lack of changes in splanchnic blood flow and mucosal $P\text{CO}_2$ or pH.

The peri- and postoperative changes in sigmoid mucosal pH during aortic surgery have been well described.[6 7 27] Sigmoid mucosal pH decreases after clamping and reaches its nadir of approximately 7.1 at 4–6 h after clamping and returns to preoperative values by the first postoperative morning. Complications can be expected if sigmoid mucosal pH does not return to pre-clamping values in 6–12 h. A sigmoid mucosal pH persistently less than 7.1 has been proposed as an early warning of problems.[7] Notably, multiple organ dysfunction syndrome (MODS) is the most common complication associated with prolonged sigmoid mucosal acidosis after aortic surgery. In our study, except for clamping-induced changes at the sigmoid mucosa, any perioperative changes in mucosal–arterial $P\text{CO}_2$ difference or arterial–gastric pH gap were related to changes in arterial $P\text{CO}_2$ or systemic acid–base balance.

Table 3 Systemic haemodynamic state and oxygen transport after surgery (mean (SD)). * Group time interaction, $P<0.05$, two-way analysis of variance for repeated measurements; † time effect, $P<0.05$, two-way analysis of variance for repeated measurements

		Baseline	2 hours
CI (litre min^{-1} m^{-2})	Epidural	3.4 (0.8)	3.4 (0.8)
	Control	3.3 (0.7)	3.3 (0.8)
MAP (mm Hg)	Epidural	90 (12)	75 (10)
	Control	94 (15)	84 (10)†
PCWP (mm Hg)	Epidural	9 (3)	10 (3)
	Control	9 (2)	7 (2)*
HR (beat min^{-1})	Epidural	77 (19)	73 (15)
	Control	80 (15)	86 (15)*
$\dot{V}o_2$ (ml min^{-1} m^{-2})	Epidural	129 (24)	131 (21)
	Control	129 (30)	135 (21)
O_2 extraction	Epidural	0.26 (0.06)	0.27 (0.03)
	Control	0.25 (0.06)	0 28 (0.06)†
Core temperature (°C)	Epidural	36.6 (1.4)	37.3 (1.4)
	Control	36.0 (1.0)	36.9 (1.2)†
Gastric–arterial $P\text{CO}_2$ difference (kPa)	Epidural	1.30 (0.80)	1.36 (0.93)
	Control	0.85 (0.61)	1.10 (0.51)
Sigmoid–arterial $P\text{CO}_2$ difference (kPa)	Epidural	1.44 (0.73)	3.31 (5.43)
	Control	2.61 (2.38)	2.25 (1.87)
Arterial–gastric pH-gap	Epidural	0.09 (0.06)	0.10 (0.07)
	Control	0.06 (0.05)	0.08 (0 04)
Arterial–sigmoid pH-gap	Epidural	0.12 (0.05)	0.19 (0 19)
	Control	0.18 (0.12)	0.17 (0.10)

In contrast with sigmoid mucosal perfusion, gastric mucosal perfusion should not be affected by vascular occlusion related to aortic surgery, and it should better reflect the patient's overall haemodynamic state. Indeed, the only mechanisms likely to influence gastric mucosal perfusion are anaesthesia and changes in systemic haemodynamics and blood volume. Our patients had no perioperative gastric mucosal acidosis, and the small reduction in gastric mucosal pH was related to changes in systemic acid–base status. This demonstrates that careful management of perioperative haemodynamics prevents gastric mucosal hypoperfusion.

In our study both gastric and sigmoid mucosal perfusion were well maintained after operation and

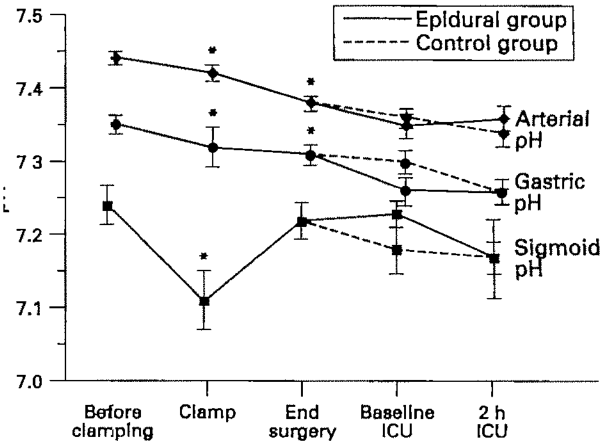

Figure 1 Arterial, gastric and sigmoid mucosal pH during the study (mean, SEM). * $P<0.05$ *vs* before clamping value (Wilcoxon).

Table 4 Splanchnic blood flow and oxygen transport after surgery (mean (SD)). * Epidural group *vs* controls, $P<0.05$, two-way analysis of variance for repeated measurements; † time effect, $P<0.05$, two-way analysis of variance for repeated measurements

		Baseline	2 h
Splanchnic blood flow (litre min^{-1} m^{-2})	Epidural	0.72 (0.28)	0.84 (0.41)
	Control	0.70 (0.21)	0.70 (0.15)
Fractional splanchnic blood flow	Epidural	0.25 (0.08)	0.22 (0.05)
	Control	0.22 (0.06)	0.21 (0.07)
Splanchnic O_2 consumption (ml min^{-1} m^{-2})	Epidural	42 (13)	39 (10)
	Control	37 (6)	37 (9)
Hepatic venous saturation	Epidural	0.63 (0.08)	0.59 (0.12)
	Control	0.63 (0.07)	0.59 (0.13)†
Splanchnic O_2 extraction	Epidural	0.35 (0.08)	0.40 (0.12)
	Control	0.34 (0.08)	0.38 (0.14)†
Arterial lactate (mmol litre^{-1})	Epidural	0.94 (0.29)	1.09 (0.43)
	Control	0.95 (0.36)	1.16 (0.45)
Hepatic venous lactate (mmol litre^{-1})	Epidural	0.45 (0.23)	0.65 (0.53)
	Control	0.59 (0.41)	0.84 (0.59)†
Hepatic lactate uptake (mmol min^{-1} m^{-2})	Epidural	0.37 (0.14)	0.31 (0.15)
	Control	0.25 (0.10)	0.20 (0.13)*

not influenced by epidural analgesia. Measurement of splanchnic blood flow was performed at the time when, according to previous studies, mucosal acidosis should have been common. Compared with previous studies, mucosal acidosis or increased mucosal–arterial CO_2 difference was remarkably rare in our study[7–9] and even patients with a high sigmoid–arterial $P\text{CO}_2$ difference did not develop serious complications. This may be because none of our patients had signs of insufficient systemic perfusion and oxygen delivery, judged either by the information provided by the invasive haemodynamic monitoring, gastric tonometry or arterial blood lactate concentrations. Unfortunately, most of the previous studies provide insufficient haemodynamic data for evaluation of systemic haemodynamic state, oxygen transport and vasoactive drugs used, and therefore it is difficult to assess if the mucosal acidosis observed in previous studies was simply a result of inadequate systemic blood flow and oxygen delivery. In our study, sigmoid–arterial $P\text{CO}_2$ difference increased remarkably in one patient during epidural analgesia. Recovery of this patient was also uneventful. The possibility that the tonometer had slid into the rectum cannot be excluded.

Changes in total hepatosplanchnic blood flow after aortic surgery have not been reported previously. The method we used does not allow assessment of the contribution of hepatic arterial and portal blood flow to total blood flow. Because of multivessel influx of the splanchnic bed and the possible heterogeneity of blood flow responses within the splanchnic bed, we cannot exclude changes in small intestine blood flow in response to epidural analgesia. Nevertheless, the lack of changes in total hepatosplanchnic blood flow and local perfusion of the mucosa, both in the upper and lower gastrointestinal tract, suggest that epidural analgesia had no effect on splanchnic perfusion in this clinical setting.

Interactions of general anaesthesia and sedation on the effects of epidural analgesia on splanchnic blood flow are unknown. Drugs used for general anaesthesia may depress the myocardium and reduce both cardiac output and splanchnic blood flow. On the other hand, vasodilatation caused by general anaesthesia may influence the splanchnic circulation. If the patients had been awake, the result may have been different because increased sympathetic activity would have been eliminated more effectively in the epidural group.

The higher lactate uptake in the epidural group was related mainly to lower hepatic venous lactate values. This may be associated with more efficient hepatic lactate uptake by the liver or lower intestinal lactate production, already at a minimum in the epidural group.

As the individual responses to any antihypertensive drug are highly variable and as both arterial pressure and its treatment may interfere with regional blood flow, we found no way of avoiding the use of different doses of sodium nitroprusside. Moreover, treatment of hypertension was considered necessary by the surgical team. We found the use of sodium nitroprusside a reasonable compromise, as we have recently shown that it does not influence fractional splanchnic blood flow in coronary artery bypass patients after surgery.[28] Mean arterial pressure decreased to a greater extent in the epidural group but it also decreased in the control group. There were no significant differences between the groups, suggesting that mean arterial pressure had no effects on splanchnic blood flow or on gastric or sigmoid pH. Another

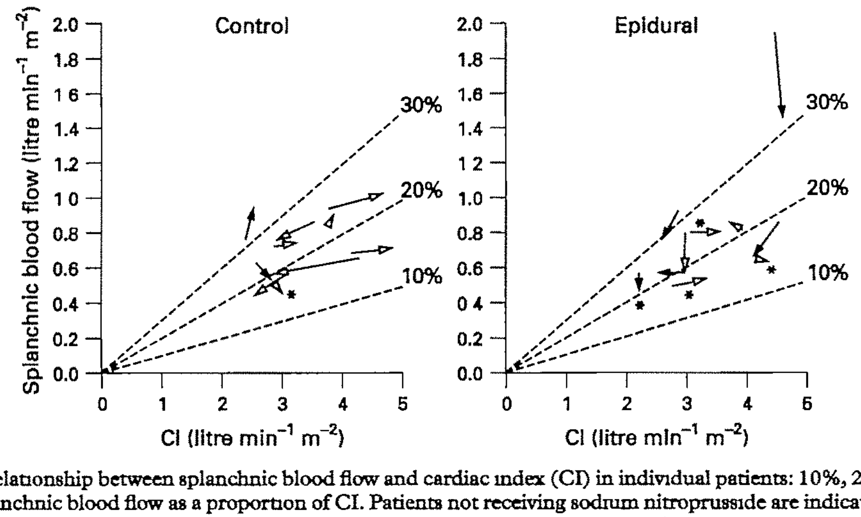

Figure 2 Relationship between splanchnic blood flow and cardiac index (CI) in individual patients: 10%, 20% and 30% lines are splanchnic blood flow as a proportion of CI. Patients not receiving sodium nitroprusside are indicated with an asterisk. Solid arrows=abdominal aortic aneurysm patients; open arrows=universal atherosclerosis patients.

potential confounding variable is the presence of both aneurysmatic and aorto-iliac occlusive patients. Despite this, the individual responses in the epidural group did not suggest any difference in the pattern of responses to epidural analgesia.

Our data suggest that epidural analgesia did not improve splanchnic perfusion in elective postoperative aortic surgery patients. Our results also showed that both gastric and sigmoid mucosal acidosis were uncommon in invasively monitored patients with a stable haemodynamic state and that short-term mucosal acidosis has no apparent effect on recovery.

Acknowledgement

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References

1. Bast TJ, van der Biezen J, Scherpenisse J, Eikelboom BC. Ischaemic disease of the colon and rectum after surgery for abdominal aortic aneurysm: a prospective study of the incidence and risk factors. *European Journal of Vascular Surgery* 1990; 4: 253–257.
2. Hagihara PF, Ernst CB, Griffen WO. Incidence of ischemic colitis following abdominal aortic reconstruction. *Surgery, Gynecology and Obstetrics* 1979; **149**: 571–573.
3. Brewster DC, Franklin DP, Cambria PR, Darling RC, Moncure AC, Lamuraglia GM, Stone WM, Abbott WM. Intestinal ischemia complicating abdominal aortic surgery. *Surgery* 1991; **109**: 447–454.
4. Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost *Intensive Care Medicine* 1994; **20**: 99–104.
5. Maynard ND, Taylor PR, Mason RC, Bihari DJ. Gastric intramucosal pH predicts outcome after surgery for ruptured abdominal aortic aneurysm. *European Journal of Vascular and Endovascular Surgery* 1996; **11**: 201–206.
6. Klok T, Moll FL, Leusink JA, Theunissen DJ, Gerrits CMJM, Keijer C. The relationship between sigmoidal intramucosal pH and intestinal arterial occlusion during aortic reconstructive surgery. *European Journal of Vascular and Endovascular Surgery* 1996; **11**: 304–307.
7. Björck M, Hedberg B. Early detection of major complications after abdominal aortic surgery: predictive value of sigmoid colon and gastric intramucosal pH monitoring. *British Journal of Surgery* 1994; **81**: 25–30.
8. Fiddian-Green R, Gantz N. Transient episodes of sigmoid ischemia and their relation to infection from intestinal organisms after abdominal aortic operations. *Critical Care Medicine* 1987; **9**: 835–839.
9. Soong CV, Blair PHB, Halliday MI, McCaigue MD, Hood JM, Rowlands BJ, Barros D'Sa AA. Bowel ischaemia and organ impairment in elective abdominal aortic aneurysm repair. *British Journal of Surgery* 1994; **81**: 965–968.
10. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increases of oxygen delivery on mortality in high-risk surgical patients. *Journal of the American Medical Association* 1993a; **270**: 2699–2707.
11. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee T-S. Prospective trial of supranormal values of survivors as therapeutic goals in high risk surgical patients. *Chest* 1988; **94**: 1176–1186.
12. Parviainen I, Ruokonen E, Takala J. Dobutamine-induced dissociation between changes in splanchnic blood flow and gastric intramucosal pH after cardiac surgery. *British Journal of Anaesthesia* 1995; 74: 277–282.
13. Uusaro A, Ruokonen E, Takala J. Gastric mucosal pH does not reflect changes in splanchnic blood flow after cardiac surgery. *British Journal of Anaesthesia* 1995; 74: 149–154.
14 Hogan QH, Stadnicka A, Stekiel TA, Bosnjak ZJ, Kampine JP. Effects of epidural and systemic lidocaine on sympathetic activity and mesenteric circulation in rabbits. *Anesthesiology* 1993; **79**: 1250–1260.
15. Hogan QH, Stekiel TA, Stadnicka A, Bosnjak ZJ, Kampine JP. Region of epidural blockade determines sympathetic and mesenteric capacitance effects in rabbits. *Anesthesiology* 1995; **83**: 604–610.
16. Fiddian-Green RG, Baker S. Predictive value of stomach wall pH for complications after cardiac operations: Comparison with other monitoring. *Critical Care Medicine* 1987; **15**: 153–156.
17. Maynard N, Atkinson S, Mason R, Smithies M, Bihari D. Influence of intravenous ranitidine on gastric intramucosal pH in critically ill patients. *Critical Care Medicine* 1994; **22** (Suppl.): A79.
18. Calvet X, Baigorri D, Ovarte M, Sawra P, Royo C, Joseph D, Mas A, Artigas A. Effect of ranitidine treatment in gastric intramucosal pH in critical patients *Intensive Care Medicine* 1998; **24**: 12–17.
19. Takala J, Keinänen O, Väisänen P, Kari A. Measurement of gas exchange in intensive care: laboratory and clinical evaluation of new device. *Critical Care Medicine* 1989; **17**: 1041–1049.
20. Uusaro A, Ruokonen E, Takala J. Estimation of splanchnic blood flow by Fick principle in man and problems in the use of indocyanine green. *Cardiovascular Research* 1995, **30**: 106–112.
21 Parviainen I, Väisanen O, Ruokonen E, Takala J. Effect of nasogastric suction and ranitidine on the calculated gastric intramucosal pH. *Intensive Care Medicine* 1996; **22**: 319–323.
22. Johansson K, Ahn H, Lindhagen J, Tryselius U. Effect of epidural anaesthesia on intestinal blood flow. *British Journal of Surgery* 1988; **75**: 73–76.
23. Sutcliffe NP, Mostafa SM, Gannon J, Harper SJ. The effect of epidural blockade on gastric intramucosal pH in the perioperative period. *Anaesthesia* 1996; **51**: 37–40.
24. Edouard AR, Degremont AC, Duranteau J, Pussard E, Berdeaux A, Samii K. Heterogeneous regional responses to simulated transient hypovolemia in man. *Intensive Care Medicine* 1994; **20**: 414–420.
25. Hendolin H, Poikolainen E, Mattila AK, Alhava E, Hanninen A, Puttonen E, Kataja M. Effect of dihydroergotamine on leg blood flow during combined epidural and general anaesthesia and postoperative deep vein thrombosis after cholecystectomy. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 288–295.
26. Nydahl P-A, Philipson L, Axelsson K, Johansson J-E. Epidural anesthesia with 0.5% bupivacaine: Influence of age on sensory and motor blockade. *Anesthesia and Analgesia* 1991: **73**: 780–786.
27. Visser WA, Liem TH, van Engmond J, Gielen MJM. Extension of sensory blockade after thoracic epidural administration of a test dose of lidocaine at three different levels. *Anesthesia and Analgesia* 1998; **86**: 332–335.
28. Kuttila K, Perttila J, Vänttinen E, Niinikoski J. Tonometric assessment of sigmoid perfusion during aortobifemoral reconstruction for arteriosclerosis. *European Journal of Surgery* 1994; **160**: 491–495
29. Parviainen I, Ruokonen E, Takala J. Sodium nitroprusside after cardiac surgery: systemic and splanchnic blood flow and oxygen transport. *Acta Anaesthesiologica Scandinavica* 1996; **40**: 606–611.

British Journal of Anaesthesia 1998; **81**: 899–901

Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine

G. LYONS, M. COLUMB, R. C. WILSON AND R. V. JOHNSON

Summary

We have compared the minimum local analgesic concentrations (MLAC) of levobupivacaine relative to racemic bupivacaine in a prospective, randomized, double-blind, sequential allocation study. Women in labour were given a 20-ml bolus of epidural levobupivacaine or bupivacaine diluted to a concentration determined by up–down sequential allocation. The initial concentration was 0.07% w/v for both drugs. Efficacy was defined using a visual analogue pain score (VAPS) at 10 mm or less within 30 min. The MLAC of levobupivacaine was 0.083% w/v (95% CI 0.065–0.101) and the MLAC of bupivacaine 0.081% w/v (95% CI 0.055–0.108). In molar terms, the MLAC of levobupivacaine was 2.87 mmol litre^{-1} (95% CI 2.25–3.49) and the MLAC of bupivacaine 2.49 mmol litre^{-1} (95% CI 1.69–3.32). With regard to the commercial preparations, the potency ratio levobupivacaine: bupivacaine was 0.98 (95% CI 0.67–1.41), and this is unlikely to be of clinical relevance. In molar terms, the ratio was 0.87 (95% CI 0.60–1.25). With regard to toxicity, the evidence should be evaluated in the light of a possible 13% potency difference in molar concentration in favour of racemic bupivacaine. (*Br. J. Anaesth.* 1998; **81**: 899–901).

Keywords: analgesia, obstetric; analgesic techniques, epidural; anaesthetics local, bupivacaine; pharmacokinetics, stereoisomers

In 1979, Albright drew attention to a number of maternal deaths after accidental i.v. injection of bupivacaine intended for the epidural space.[1] In the UK, the problem manifested itself in deaths during i.v. regional anaesthesia (IVRA) with bupivacaine.[2] Subsequent recommendations led to the withdrawal of bupivacaine for IVRA, and the 0.75% w/v concentration for obstetric use. Animal studies have shown that the adverse cardiac effects of bupivacaine are more difficult to reverse than those of lidocaine (lignocaine),[3] and attention has since been directed towards developing local anaesthetics that have less potential for cardiotoxicity.

Bupivacaine is a racemic mixture consisting of equal quantities of the optical isomers, levobupivacaine and dexbupivacaine, also known as the S(-) and R(+) enantiomers. For more than 25 yr it has been known that the two enantiomers of bupivacaine have different activities, and that animal studies have shown levobupivacaine to be less toxic than both dexbupivacaine and racemic bupivacaine.[4] Toxicity comparisons are conducted on a weight for weight basis, and toxicity ratios determined in the laboratory are not valid for clinical practice if differences in analgesic potencies require different dosing regimens.

The aim of this study was to determine the relative analgesic potencies of levobupivacaine and racemic bupivacaine using the minimum local analgesic concentration (MLAC) model, in women requesting epidural pain relief in labour.[5]

Patients and methods

After obtaining approval from the Hospital Ethics Committee for this randomized, double-blind, parallel group, sequential allocation study and after obtaining informed consent, we studied ASA I women requesting epidural pain relief in the first stage of labour. We excluded those in whom cervical dilatation exceeded 5 cm and those who had received opioid or sedative drugs. The use of a transcutaneous electrical nerve stimulator or Entonox before epidural request was not regarded as a need to exclude.

I.v. saline 0.9% w/v was infused via a forearm cannula. The epidural space was found using an 18-gauge Tuohy needle at either L2–3 or L3–4 in the sitting position. Loss of resistance to saline was used to identify the epidural space, limiting injection to 2 ml in order to minimize dilution of local anaesthetic. For the purpose of the study, the test dose was omitted.

The first administration of levobupivacaine or bupivacaine was in a freshly prepared syringe containing 20 ml of test solution given over 5 min. Local anaesthetic was diluted with 0.9% w/v saline to achieve the desired concentration at room temperature.

Women were allocated randomly to one of two concurrent groups to receive levobupivacaine (n=30) or bupivacaine (n=30). The concentration of local anaesthetic in the first syringe of each group was 0.07% w/v. This corresponded to a previously determined MLAC for bupivacaine.[5] Thereafter, the concentration of the test solution in each individual syringe was determined by the response of the previous patient in the same group to the higher or lower concentration in her test syringe, according to up–down sequential allocation. Maternal heart rate, arterial pressure, uterine contractions and fetal heart rate were monitored.

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Efficacy of the first dose was assessed using a 100-mm visual analogue pain score (VAPS) where 0 represented "no pain" and 100, "worst pain ever", at 5-min intervals up to 30 min after injection of the test solution (first bolus). Three outcomes were possible: (1) *effective*, this required that the VAPS decreased to 10 mm or less at the height of contraction, within 30 min, and indicated the end of the study and directed a decrement of 0.01% w/v local anaesthetic for the next woman; (2) *ineffective*, this followed failure of the VAPS to reach 10 mm within 30 min of the test solution. Rescue analgesia consisting of 0.25% bupivacaine 15 ml was given. After this, a reduction in VAPS to 10 mm or less indicated the end of the study and directed a 0.01% increment for the next woman; (3) *repeat*, failure to achieve a VAPS of 10 mm after rescue directed that the same concentration be repeated for the next woman.

For all women, age, weight, height, gestation, parity, cervical dilatation, use of oxytocin infusion and presence of pruritus were recorded.

A modified Bromage score (0=no impairment, 1=inability to raise leg, 2=inability to flex knee and 3=complete paralysis) was performed on all women, either at 30 min after an effective outcome or after rescue when an ineffective outcome had been reached. If the score for both legs was zero, women were mobilized and ability to stand unaided, walk unaided and perform a knee bend[6] was recorded.

The source of racemic bupivacaine was the commercial preparation (Marcain, Astra) expressed as anhydrous bupivacaine hydrochloride containing 2.64 mg ml^{-1} of bupivacaine hydrochloride monohydrate corresponding to 2.12 mg ml^{-1} (7.7 mmol litre^{-1}) of free base. The source of levobupivacaine (Chirocaine, Chiroscience) was expressed as anhydrous pure base containing 2.50 mg ml^{-1} (8.6 mmol litre^{-1}) of free base.

Patient and obstetric data were collected and are presented as mean (SD) and median (interquartile range), as appropriate. Median effective concentrations were estimated from the up–down sequences using the formula of Dixon and Massey which enabled MLAC with 95% confidence interval (95% CI) to be derived.[7] Further analyses included the unpaired Student's t test and Mann Whitney U test for between-group comparisons of parametric and non-parametric data, respectively, with Fisher's exact test for categorical data.[8 9] Analyses were carried out using the following software: Microsoft Excel 5.0a for Windows, Statistical Package for the Social Sciences (SPSS) 6.1 for Windows, GraphPad Instat 2.05a for DOS and Pharmacologic Calculation System (PCS) 4.2 for DOS.

Results

We enrolled 73 women in the study. Six women in each group were withdrawn because of study violations, and one patient in the bupivacaine group because of failure of rescue. Thus 60 women were evaluated. The groups were similar in patient and obstetric characteristics (table 1).

Using the formula of Dixon and Massey, the MLAC of levobupivacaine was 0.083% w/v (95% CI 0.065–0.101) and the MLAC of racemic bupivacaine 0.081% w/v (95% CI 0.055–0.108) The relative potency of levobupivacaine to racemic bupivacaine was 0.98 (95% CI 0.67–1.41) (figs 1, 2).

Table 1 Patient and obstetric data (mean (SD), median [interquartile range] or number). VAPS=Visual analogue pain scores

	Bupivacaine (n=30)	Levobupivacaine (n=30)
Age (yr)	26.9 (18–37)	26.8 (18–35)
Height (cm)	163 (6.52)	163 (6.67)
Weight (kg)	77.5 (14.9)	75.4 (12.5)
Gestation (weeks)	39 [39–40]	40 [40–41]
Cervical dilatation (cm)	3 [3–4]	3 [2–3]
Parity	0 [0–1]	0 [0–1]
Nulliparous/multiparous	16/14	21/9
Oxytocin infused	7	12
Initial VAPS (mm)	66 [45–84]	72 [46–89]

In terms of molar concentrations, the MLAC of levobupivacaine was 2.87 (95% CI 2.25–3.49) mmol litre^{-1} and the MLAC of racemic bupivacaine 2.49 (95% CI 1.69–3.32) mmol litre^{-1}. The molar potency ratio was 0.87 (95% CI 0.60–1.25). The derived dose–response point estimates are illustrated in figure 3.

Fifteen women in the levobupivacaine group had motor scores of 0 compared with 12 after racemic bupivacaine (ns). All women with 0 scores were able to stand and walk unaided, and perform a knee bend.

Discussion

We have shown a 2% difference in potency between the two commercial preparations in favour of racemic bupivacaine. This is unlikely to be of clinical relevance. Levobupivacaine is bound by Directive 91/507 of the European Economic Community, part 2, section A, clause 3.3, which stipulates that formulations of hydrates and salts must be expressed as milligrams of active moiety. Our ampoules of levobupivacaine 0.25% w/v contained 2.5 mg ml^{-1} of free base. Registration of racemic bupivacaine predates this directive, and an ampoule of the same concentration contains bupivacaine hydrochloride 2.5 mg ml^{-1}. Because of this, an ampoule of levobupivacaine contains 11% more molecules of local anaesthetic than an ampoule of the same concentration of bupivacaine, and when this is taken into account, the potency difference widens to 13%. Although the Directive is only applicable to countries in the

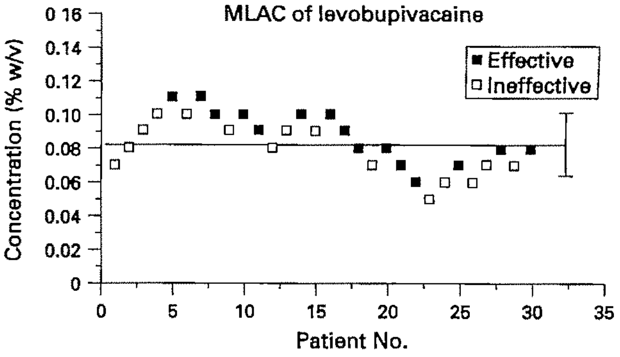

Figure 1 EC$_{50}$ values (mean, 95% confidence interval) for levobupivacaine, determined by up–down sequential allocation. Testing interval was 0.01 % w/v. The MLAC of levobupivacaine was 0 083% w/v (95% CI 0.065–0.101).

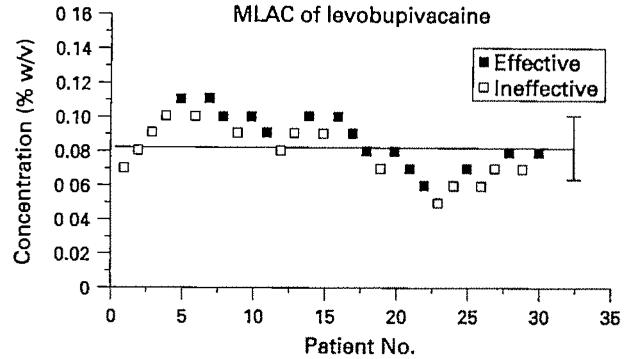

Figure 2 EC_{50} values (mean, 95% confidence interval) of bupivacaine, determined by up–down sequential allocation. Testing interval was 0.01 % w/v. The MLAC of bupivacaine was 0.081% w/v (95% CI 0.55–0.108).

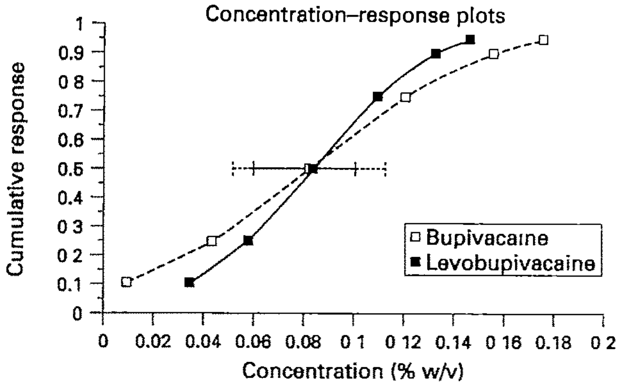

Figure 3 EC_{50} values (mean, 95% confidence interval) for levobupivacaine and bupivacaine. Derived point estimates are plotted to demonstrate the concentration–response relationship.

European Community, it is likely that the European formulation will become universal.

Another potency comparison was that of Aps and Reynolds[10] who conducted an intradermal study with levobupivacaine and dexbupivacaine in human volunteers. They found that levobupivacaine was more potent. This can be explained by differences in vasoactivity. There is a tendency for S(-) enantiomers to produce more vasoconstriction at low concentrations, and this could explain the finding.[10] The addition of vasoconstrictors to epidural bupivacaine has little clinical effect[11] and gives reason to believe that performance in the epidural space is unlikely to be influenced by vasoconstriction.

Toxicity studies performed in animals have shown that both the convulsive and lethal doses of the S(-) enantiomer are greater than those for racemic bupivacaine.[12 13] When given i.v. to 12 human volunteers at a rate of 10 mg min^{-1}, plasma concentrations of levobupivacaine and racemic bupivacaine at the end of the infusion were 2.38 μg ml^{-1} and 1.87 μg ml^{-1}, respectively. Mean total tolerated doses were 54 mg of levobupivacaine and 45.6 mg of racemic bupivacaine. Thoracic bioimpedance recorded decreases in stroke index, acceleration index and ejection fraction that were greater with racemic bupivacaine compared with levobupivacaine, and this difference was statistically significant.[14] In this study, the dosing regimen was adjusted to accommodate differences in weight/volume expression between the local anaesthetics.

In summary, we have shown that with regard to commercial preparations, levobupivacaine was 2% less potent than racemic bupivacaine, but this is unlikely to be clinically important. Because of differences in the weight/volume expression of the two local anaesthetics, there is a possible 13% difference in the potencies of the molar concentrations, and this must be borne in mind when toxicity studies are evaluated.

Acknowledgement

This study was commissioned by Chiroscience who supplied Chirocaine (0.25% w/v levobupivacaine as the hydrochloride salt).

References

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; 51: 285–291.
2. Heath ML. Deaths after intravenous regional anaesthesia *British Medical Journal* 1982; 285: 913–914.
3. Santos AC, Pedersen H, Finster M. Local anesthetics. In: Chestnut DH, ed. *Obstetric Anesthesia* St Louis: Mosby, 1994; 207.
4. Aberg G. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. *Acta Pharmacologica et Toxicologica* 1972; 31: 273–286.
5. Columb MO, Lyons G. Determination of the minimum local analgesic concentrations of epidural bupivacaine and lidocaine in labor. *Anesthesia and Analgesia* 1995; 81. 833–837.
6. Breen TW, Shapiro T, Glass B, Foster-Payne D, Oriol N. Epidural anesthesia for labor in an ambulatory patient. *Anesthesia and Analgesia* 1993; 77: 919–926.
7. Dixon WJ, Massey FJ. *Introduction to Statistical Analysis*, 4th Edn. New York: McGraw-Hill, 1983; 428–439.
8. Armitage P, Berry G *Statistical Methods in Medical Research*, 3rd Edn Oxford: Blackwell Scientific Publications, 1994; 136–141.
9. Altman DG. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1991; 212–213
10. Aps C, Reynolds F. An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine. *British Journal of Clinical Pharmacology* 1978; 6: 63–68.
11. De Jong RH. *Local Anesthetics*. St Louis: Mosby, 1994; 158–161
12. Aberg G Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. *Acta Pharmocologica et Toxicologica* 1972; 31: 273–286.
13. Luduena FP, Bogado EF, Tullar BF. Optical isomers of mepivacaine and bupivacaine. *Archives Internationales de Pharmacodynamie et de Therapie* 1972; 200: 359–369.
14. Gristwood R, Bardsley H, Baker H, Dickens J Reduced cardiotoxicity of levobupivacaine compared with racemic bupivacaine (Marcain): New clinical evidence. *Expert Opinion in Investigational Drugs* 1994; 3: 1209–1212.

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Are changes in the evoked electromyogram during anaesthesia without neuromuscular blocking agents caused by failure of supramaximal nerve stimulation?†

S. L. POLHILL, F. CLEWLOW AND D. C. SMITH

Summary

The evoked electromyogram often decreases during anaesthesia in the absence of neuromuscular block. We have measured the electromyogram of the first dorsal interosseous muscle evoked by train-of-four stimulation of the ulnar nerve in 63 patients undergoing anaesthesia for minor surgery. We used Medicotest P-00-S electrodes, a Datex Relaxograph and a current sink in the stimulating leads in parallel with the current path through the patient. The current sink was used to shunt some of the maximum available output current from the Relaxograph while maintaining the supramaximal stimulus current passing through the patient. After 30 min of anaesthesia, when the muscle response to train-of-four was stable, the ulnar nerve stimulus current was increased by reducing the proportion shunted through the current sink. The electromyographic response did not change during the study in 13 patients. In the remaining 50 patients, the response decreased to 78.4% (SD 27.1%, range 7.5–95.0%) of baseline values over the first 20 min of anaesthesia. In 22 of these patients, the electromyographic response increased from 71.4 (SD 22.6)% to 92.3 (9.5)% of baseline responses when the stimulus current was increased by 12.3 (2.4) mA, while in the remaining 28 patients the response decreased to 83.7 (10.6)% and did not increase with increasing stimulus current. These results suggest that loss of supramaximal stimulation is partly responsible for the observed changes in the evoked electromyogram during anaesthesia. (*Br. J. Anaesth.* 1998; **81**: 902–904).

Keywords: measurement techniques, electromyography; measurement techniques, neuromuscular block; neuromuscular block, measurement of response

The evoked electromyogram (EEMG) often fails to return to baseline values during offset of neuromuscular block. In patients who have not received a neuromuscular blocking drug, the EEMG response may also decrease to approximately 80% of control values over the first 20 min of anaesthesia,[2 3] but the response does not decrease with time in awake subjects.[1] Improper fixation of the recording electrodes[4] and changes in forearm position[5] may alter the EEMG response, possibly by alteration of the position of the stimulating electrodes relative to the ulnar nerve. If movement of the stimulating electrodes results in failure of supramaximal nerve stimulation, by simply increasing the stimulus current the EEMG response should increase towards the control value set at initial calibration.

To study the effect of stimulus current on the EEMG response during anaesthesia, we wished to be able to increase the output current from the nerve stimulator of a Relaxograph (Datex, Helsinki) after calibration, without changing the calibration values for the train-of-four responses in the memory of the Relaxograph. The Relaxograph stimulus current can be changed after calibration, but only in discrete steps of varying magnitude. Therefore, we decided to use a calibrated adjustable current sink in parallel with the stimulator output leads. This adjustable current sink was designed by Mr F. Clewlow along conventional lines, to have a sink capability of 40 mA at a maximum input voltage of 400 V and be capable of a square wave response to a current pulse of 100 μs duration. Its performance was independent of stimulus electrode impedance. Details of the device are available from the authors on request. The current sink shunts a variable proportion of the Relaxograph output current away from the patient during calibration, while the supramaximal stimulus current reaching the patient is maintained (fig. 1). The proportion of shunted current can later be reduced, increasing the current passing through the stimulating electrodes to the patient.

Patients and methods

After obtaining approval from Southampton Joint Ethics Committee, we studied 63 adult patients, ASA I or II, body mass index (weight/height^2) <27, undergoing minor surgery which did not require a neuromuscular blocking drug during anaesthesia. Premedication was given at the discretion of the responsible anaesthetist.

We recorded the EEMG over the belly of the first dorsal interosseous muscle with the Relaxograph and Medicotest P-00-S electrodes. The indifferent electrode was on the proximal phalanx of the index finger. We stimulated the ulnar nerve at the wrist, with

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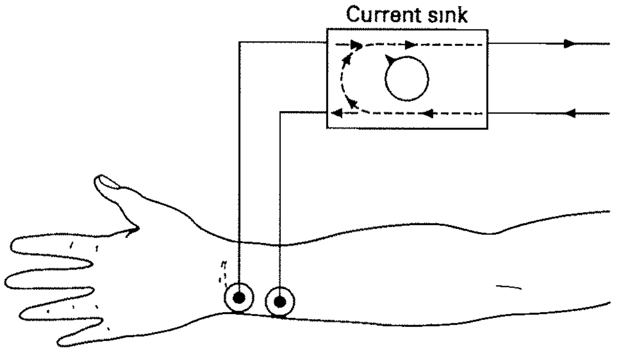

Figure 1 Operating principle of the current sink. During calibration of the Relaxograph, the sink shunts a variable proportion of the stimulus current to ground, bypassing the patient. The amount of shunted current may later be reduced, increasing the stimulus current to the patient.

the ground electrode over the median nerve at the proximal wrist crease. Electrode sites were degreased for 5 s with gauze and 70% isopropyl alcohol. The arm was laid on an armboard in 90° abduction with the elbow flexed to 30°, and was loosely fixed in position with adhesive tape. The arm was left exposed on the armboard; theatre temperature was regulated to 22°C. Routine monitoring comprised pulse oximetry, non-invasive arterial pressure and ECG.

Anaesthesia was induced with propofol 2–2.5 mg kg^{-1}, and a laryngeal mask was inserted. Anaesthesia was maintained with 1–1.5% isoflurane and 66% nitrous oxide in oxygen, with the patient breathing spontaneously via a Mapleson A system. We started EEMG monitoring at the loss of the eyelash reflex during induction of anaesthesia. The Relaxograph was switched on and the automatic calibration routine determined the supramaximal stimulus current. The difference between the supramaximal stimulus current and the 70 mA maximum output from the Relaxograph was then dialled on the control knob of the current sink. We then recalibrated the Relaxograph to ensure that the output current from the Relaxograph was close to 70 mA while the original supramaximal stimulus current to the patient was maintained, with the maximum possible current passing through the current sink. We did not measure the actual stimulus current to the patient, but the Relaxograph and current sink had both been calibrated in the laboratory before the study began. The patient was then transferred carefully from the anaesthetic room to the operating theatre. The Relaxograph continued to measure the train-of-four response every 20 s for the duration of the study. After 30 min we adjusted the current sink to increase the stimulus current to the patient in an attempt to restore the T1 response to 100%. We repeated the Relaxograph calibration routine, without using the current sink, at the end of monitoring in 45 of the patients.

We analysed the data using a computer spread sheet (Excel v4.0, Microsoft). Results are presented as mean (SD). We regarded a 5% change in either direction from baseline EEMG responses as a clinically significant change.

Results

Patients were aged 22–68 yr, with a 50:50 male: female ratio. The T1 response remained stable within ±5% of the control response in 13 of the 63 patients. In these patients the T1 response did not increase when additional stimulus current was passed through the electrodes, and the supramaximal stimulus current did not change between initial calibration and recalibration at the end of the study.

In 50 patients the T1 response decreased to 78.4 (27.1)% of baseline responses over the first 20 min of anaesthesia. These 50 patients were divided into two groups (A and B) according to their response to increased stimulus current:

Group A (22 of 50 patients). Mean T1 response decreased to 71.4 (22.6)% (range 7.5–95.0%) of control over the first 20 min of anaesthesia and remained stable thereafter. Increasing the amount of current passing through the stimulus electrodes by 12.3 (2.4) mA increased the T1 response to 92.3 (9.5)% of control (fig. 2). In four of these patients the new supramaximal stimulus current was greater than the 70 mA maximum output from the Relaxograph and could not be determined, while in the other 18 patients the mean supramaximal stimulus current increased from 52.5 mA at initial calibration to 64.8 mA at recalibration.

Group B (28 of 50 patients). Mean T1 response decreased to 83.7 (10.6)% (range 47.5–95.0%) of control over the first 20 min of anaesthesia and remained stable thereafter. Increasing the stimulus current by 12.3 (2.4) mA did not increase the T1 response (fig. 2). The mean supramaximal stimulus current at initial calibration was 47.1 mA, and after recalibration, 49.7 mA.

There was no difference in age, body mass index or sex distribution between the subgroups which could account for these differences in T1 response.

Discussion

The decrease in EEMG response from the calibration baseline was similar to that reported previously.[2 6 7] This has largely been ignored in the past, although some workers reject those recordings in which the EEMG response does not return to within 10–15% of baseline values[8] and others allow the EEMG to stabilize for 20 min before recalibrating the response

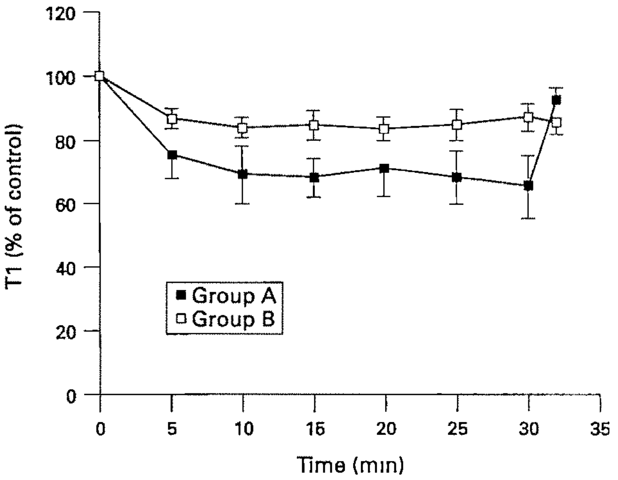

Figure 2 Mean changes in the evoked electromyographic response during anaesthesia in groups A and B. Stimulus current was increased at 30 min. Error bars represent 95% confidence interval for the mean value.

to 100%.[9] We found that the EEMG response was not often restored to the 100% baseline value with additional stimulus current, although the variability of the response about the mean value was reduced. In those patients in whom the T1 response did not change during the study, we cannot assume that there was no change in the *maximal* nerve stimulation current, as any change may simply be hidden within the 20% margin of the *supramaximal* stimulus current.

The decrease in the EEMG response during anaesthesia is unrelated to changes in the electrical impedance of the stimulus or recording electrodes,[10 11] but is associated with a reduction in the area and amplitude, but not duration, of the evoked compound action potential.[12] This implies either that the decrease in the EEMG response results from a decrease in the number of active motor units, or that the end-plate depolarization current is reduced during anaesthesia.

Increasing the distance between the stimulus electrode and nerve reduces the stimulating current density reaching the nerve by the fourth power of the distance, as the current flows in three dimensions through the tissues, which may allow the effective stimulus current to become submaximal. Movement of the stimulating electrodes relative to the ulnar nerve may result from pronation or supination of the forearm during the procedure,[5] possibly during repositioning of the patient during surgery.[13] Alternatively, the volume of the soft tissues of the forearm may increase as a result of vasodilatation during anaesthesia. Obese patients have greater distances between the stimulating electrodes and nerve than slimmer patients, and therefore obese patients may be more susceptible than thin patients to decreases in the EEMG control response during anaesthesia. We excluded obese patients from our study.

Volatile anaesthetic agents may modify neuromuscular transmission by reducing acetylcholine output from the motor nerve terminal, although routine concentrations of volatile anaesthetics do not modify either the motor nerve or muscle membrane thresholds for depolarization.[14] Isoflurane at concentrations greater than 1.25 MAC and enflurane at concentrations greater than 3.5% induce tetanic fade and depress the mechanical single twitch response by 10% in humans.[15 16] The mechanism for this is unclear. More standard concentrations of halothane and isoflurane increase the mechanical twitch response but decrease the EEMG response in humans, but the mechanical response recovered on cessation of anaesthesia while the EEMG response did not.[17 18]

In summary, the decrease in the control response of the EEMG during anaesthesia was caused, at least in part, by failure of supramaximal stimulation of the motor nerve. However, we cannot explain why increasing the stimulus current increased the T1 response in only 44% of those patients in whom it decreased, and further work is required to provide a complete solution to this problem.

References

1. Fisher W, Smith DC. The EEMG in awake subjects. *British Journal of Anaesthesia* 1994; 73: 261.
2. Edmonds HL, Paloheimo M, Wauquier A. *Computerized EMG Monitoring in Anaesthesia and Intensive Care*. Weert: Malherbe Publishing Group, 1988.
3. Meretoja OA, Brown TCK. Drift of the evoked thenar EMG signal. *Anesthesiology* 1989; 71: A825.
4. Edmonds HL, Paloheimo M. Computerized monitoring of the EMG and EEG during anaesthesia. An evaluation of the anesthesia and brain activity monitor (ABM). *International Journal of Clinical Monitoring and Computing* 1985; 1: 201–210.
5. Smith DC, Booth JV. The influence of muscle temperature and forearm position on evoked electromyography of the hand. *British Journal of Anaesthesia* 1994; 72: 407–410.
6. Lam C, Cass NM, Ng KC. Electromyographic monitoring of neuromuscular block. *British Journal of Anaesthesia* 1981; 53: 1351–1357.
7. Kopman AF. The relationship of evoked electromyographic and mechanical responses following atracurium in humans. *Anesthesiology* 1985; 63: 208–211.
8. Power SJ, Jones RM. Reversal of profound paralysis: Use of large doses of edrophonium to antagonise vecuronium and pancuronium induced neuromuscular blockade. *Acta Anaesthesiologica Scandinavica* 1989; 33: 478–481.
9. Meretoja OA, Werner MU, Wirtavouri K, Luosto T. Comparison of thumb adduction and thenar EMG in a pharmacodynamic study of alcuronium. *Acta Anaesthesiologica Scandinavica* 1989; 33: 545–548.
10. Smith DC. Changes in recording electrode impedance during anaesthesia have no effect on evoked electromyographic responses. *European Journal of Anaesthesiology* 1993; 10: 371–374.
11. Smith DC, Tan S, Follett DH. Effects of skin temperature on skin-electrode impedance at high direct current density. *Journal of Medical Engineering and Technology* 1992; 16: 210–213.
12. Smith DC, Seavell CR. Effect of neuromuscular block on the shape of the evoked electromyogram. *British Journal of Anaesthesia* 1995; 75: 651–652P.
13. Kosek PS, Sears DH, Rubenstein EH. Minimizing movement-induced changes in twitch response during integrated electromyography. *Anesthesiology* 1988; 69: 142–143.
14. Ngai SH, Hanks EC, Farhie SE. Effects of anesthetics on neuromuscular transmission. *Anesthesiology* 1965; 26: 162–167.
15. Lebowitz MH, Blitt CD, Walts LF. Depression of twitch response to stimulation of the ulnar nerve during Ethrane anesthesia in man. *Anesthesiology* 1970; 33: 52–57.
16. Miller RD, Eger EI, Way WL, Stevens WC, Dolan WM. Comparative neuromuscular effects of Forane and halothane alone and in combination with d-tubocurarine in man. *Anesthesiology* 1971; 35: 38–42.
17. Nilsson E, Paloheimo M, Muller K, Heinonen J. Halothane-induced variability in the neuromuscular transmission of patients with myasthenia gravis. *Acta Anaesthesiologica Scandinavica* 1989; 33: 395–401.
18. Nilsson E, Muller K. Neuromuscular effects of isoflurane in patients with myasthenia gravis. *Acta Anaesthesiologica Scandinavica* 1990; 34: 126–131.

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LABORATORY INVESTIGATIONS

Effects of enflurane, isoflurane, sevoflurane and desflurane on reperfusion injury after regional myocardial ischaemia in the rabbit heart *in vivo*

B. PRECKEL, W. SCHLACK, T. COMFÈRE, D. OBAL, H. BARTHEL AND V. THAMER

Summary

It is known that volatile anaesthetics protect myocardial tissue against ischaemic and reperfusion injury *in vitro*. In this investigation, we have determined the effects of the inhalation anaesthetics, enflurane, isoflurane, sevoflurane and desflurane, administered only during early reperfusion, on myocardial reperfusion injury *in vivo*. Fifty chloralose-anaesthetized rabbits were subjected to 30 min of occlusion of a major coronary artery followed by 120 min of reperfusion. Left ventricular pressure (LVP, tip-manometer), cardiac output (CO, ultrasonic flow probe) and infarct size (triphenyltetrazolium staining) were determined. During the first 15 min of reperfusion, five groups of 10 rabbits each received 1 MAC of enflurane (enflurane group), isoflurane (isoflurane group), sevoflurane (sevoflurane group) or desflurane (desflurane group), and 10 rabbits served as untreated controls (control group). Haemodynamic baseline values were similar between groups (mean LVP 106 (SEM 2) mm Hg; CO 281(7) ml min^{-1}). During coronary occlusion, LVP and CO were reduced to the same extent in all groups (LVP 89% of baseline; CO 89%). Administration of inhalation anaesthetics during early reperfusion further reduced both variables, but they recovered after discontinuation of the anaesthetics to values not different from control animals. Infarct size was reduced from 49 (5)% of the area at risk in the control group to 32 (3)% in the desflurane group (*P*=0.021), and to 36 (2)% in the sevoflurane group (*P*=0.097). In the enflurane group, infarct size was 39 (5)% (*P*=0.272). Isoflurane had no effect on infarct size (48 (5)%, *P*=1.000). The results show that desflurane and sevoflurane markedly reduced infarct size and therefore can protect myocardium against reperfusion injury *in vivo*. Enflurane had only a marginal effect and isoflurane offered no protection against reperfusion injury *in vivo*. These different effects suggest different protective mechanisms at the cellular level. (*Br. J. Anaesth.* 1998; **81**: 905–912).

Keywords: anaesthetics, volatile, enflurane; anaesthetics, volatile, isoflurane; anaesthetics, volatile, sevoflurane; anaesthetics, volatile, desflurane; heart, ischaemia; heart, myocardial function, rabbit

The term "lethal reperfusion injury" characterizes a situation in which myocardium losses viability by pathomechanisms that are triggered by restoration of oxygen and substrate supply after myocardial ischaemia.[1] It has been demonstrated that halothane administration only during the early reperfusion period can protect isolated cardiomyocytes and isolated rat hearts against reperfusion injury.[2 3] This protective effect of halothane was confirmed in an *in vivo* rabbit model of coronary artery occlusion and subsequent reperfusion, and was independent of the haemodynamic side effects of halothane.[4] Although several studies have examined the effects of the commonly used volatile anaesthetics, halothane, enflurane and isoflurane, in myocardial ischaemia,[5–7] little is known of the specific influence of these agents on myocardial reperfusion injury.[4] In addition, the influence of the new volatile anaesthetics, sevoflurane and desflurane, on reperfusion injury *in vivo* has yet to be described. In the isolated rat heart, improvement of myocardial function was observed after 30 min of ischaemia followed by 60 min of reperfusion if inhalation anaesthetics were administered during early reperfusion.[8 9] However, the time course of creatine kinase release (as a marker of cellular injury) and recovery of left ventricular (LV) developed pressure (as an index of myocardial function) varied depending on the inhalation anaesthetic used.[8 9]

We hypothesized that enflurane, isoflurane, sevoflurane and desflurane can protect the myocardium against reperfusion injury *in vivo* in a similar manner to halothane. Therefore, we designed this study to determine the effects of these volatile anaesthetics on reperfusion injury in the *in situ* rabbit heart with regional coronary artery occlusion and subsequent reperfusion. Baseline anaesthesia was maintained with continuous infusion of chloralose during the experiments and the volatile anaesthetics were administered only during the initial reperfusion period (15 min) to determine specific actions against reperfusion injury. Infarct size was determined by triphenyltetrazolium chloride (TTC) staining after 2 h of reperfusion.

Materials and methods

The study was performed in accordance with the regulations of the German Animal Protection Law and

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after obtaining permission from the Animal Care Committee of the District of Düsseldorf.

ANIMAL PREPARATION

The animal preparation has been described in detail previously.[4] In brief, 50 New Zealand White rabbits (body weight 2.8–4.4 (mean 3.6) kg) were anaesthetized with sodium thiopental (thiopentone) 15–30 mg kg^{-1}. After intubation of the trachea, anaesthesia was maintained by continuous infusion of α-chloralose 40 mg kg^{-1} h^{-1} and the lungs ventilated artificially. The rabbits were instrumented for measurement of aortic pressure (AOP, Statham transducer, PD23, Gould, Cleveland, OH, USA), LV pressure (Micro-Tip Pressure Transducer, Sensodyn S PO SF-1, Braun Melsungen AG, Melsungen, Germany) and cardiac output minus coronary flow volume (CO, 4S or 6S ultrasonic flow probe, T 208, Transonic Systems Inc., Ithaca, NY, USA). A snare was passed around a major coronary artery for later occlusion. Temperature was measured inside the pericardial cradle (GTH 1160, Digital Thermometer, Geisinger Electronic, Germany) and maintained at 38.5±0.3°C by adjusting a heating pad and an infrared lamp.

EXPERIMENTAL PROCEDURE

Fifteen minutes after completion of the surgical preparation, baseline measurements were performed. In eight rabbits, the inhalation anaesthetics were given in a randomized order at concentrations of 0.5, 1.0 and 1.5 MAC, in order to assess the haemodynamic effects of the anaesthetics on normal rabbit myocardium in this experimental preparation under chloralose anaesthesia. After discontinuation of the volatile anaesthetic, at least 30 min were allowed until haemodynamic values recovered to baseline before the next agent was applied. For the ischaemia–reperfusion experiments, the prepared coronary artery was occluded after baseline measurements by tightening the snare. The effectiveness of this manoeuvre was verified by the appearance of epicardial cyanosis and changes in surface electrocardiogram. Ventricular fibrillation during coronary occlusion was treated by electrical defibrillation (5 J, DCS261 Defibrillator, Piekser, Ratingen, Germany). After 30 min of occlusion, the snare occluder was released. Reperfusion was verified by the disappearance of epicardial cyanosis. After 120 min of reperfusion, the heart was arrested by injection of potassium chloride solution into the left atrium and quickly excised. The area at risk size was then determined by Evans blue staining of the non-ischaemic area, and infarct size within the area at risk was determined by TTC staining. The procedure has been described in detail previously.[4]

Ten rabbits underwent the ischaemia–reperfusion procedure without further intervention (control group). Eight of these rabbits also served as controls in a previous study.[4] In 10 rabbits, enflurane, isoflurane, sevoflurane or desflurane (Vapor 19.3, Devapor, Drägerwerke AG, Lübeck, Germany) was added to the inspired gas starting 3 min before reperfusion to achieve a stable concentration at the beginning of the reperfusion period and was continued for the first 15 min of reperfusion. The volatile anaesthetics were titrated to an end-tidal concentration of 2.8% enflurane (enflurane group), 2.0% isoflurane (isoflurane group), 3.7% sevoflurane (sevoflurane group) and 8.9% desflurane (desflurane group) (Datex Capnomac Ultima, Division of Instrumentarium Corp., Helsinki, Finland), which corresponded to 1.0 MAC of the respective volatile anaesthetics in the rabbit.[10-12]

DATA ANALYSIS

LV pressure, its first derivative d*P*/d*t*, AOP and stroke volume were recorded continuously on an ink recorder (Recorder 2800, Gould Inc., Cleveland, OH, USA) and stored on a videotape recorder (SL-C 30 PS, Sony, Tokyo, Japan) using pulse code modulation (VPMD 8–12, Fa. Heim, Bergisch Gladbach, Germany) for later playback and analysis. The data were digitized using an analogue to digital converter (Data Translation, Marlboro, MA, USA) at a sampling rate of 500 Hz and processed later on a personal computer.

Haemodynamic variables

Global systolic function was measured in terms of LV peak systolic pressure (LVPSP) and maximum rate of pressure increase (d*P*/d*t*max). Global LV end-systole was defined as the point of minimum d*P*/d*t*,[13] and LV end-diastole as the beginning of the sharp upslope of the LV d*P*/d*t* tracing. The time constant of decrease in LV isovolumic pressure (τ) was used as an index of LV diastolic function.[14] CO was calculated from stroke volume and heart rate, rate pressure product (RPP) from heart rate and LVPSP, and systemic vascular resistance (SVR) from mean AOP and CO, assuming a right atrial pressure of 0 mm Hg in the open-chest preparation.

Statistical analysis

Data are presented as mean (SEM). The effects of inhalation anaesthetics on normal myocardium were assessed by one-way analysis of variance (ANOVA) for repeated observations. In the ischaemia–reperfusion experiments, statistical analysis was performed by two-way ANOVA for time and treatment (experimental group) effects. If an overall significant effect between groups was found, comparison was made for each time using one-way ANOVA followed by the Dunnett's post-test, where appropriate. Differences in the influence of area at risk size on infarct size were determined by ANOVA for differences between regression slopes, followed by analysis of covariance.[15] Some of the control animals were from a previous study.[4] Therefore, the two treatment groups of the previous study were included in the statistical evaluation to prevent an increase in type I error by repeated use of the same controls.

Results

A total of 63 animals were used. Five animals died from ventricular fibrillation during coronary artery occlusion. In the remaining 58 animals, complete data sets were obtained (control group, *n*=10; enflurane group, *n*=10; isoflurane group, *n*=10; sevoflu-

Table 1 Effects of increasing doses of enflurane, isoflurane, desflurane, and sevoflurane on normal myocardium were tested during α-chloralose anaesthesia. LVPSP = left ventricular peak systolic pressure, CO = cardiac output; d*P*/d*t*max = maximum rate of left ventricular pressure increase, SVR = systemic vascular resistance

	Baseline	0.5 MAC	1.0 MAC	1.5 MAC
LVPSP (mm Hg)		(%)	(%)	(%)
Enflurane	106 (6.1)	87 (5.4)	70 (8.0)	45 (2.1)
Isoflurane	107 (6.6)	98 (3.3)	88 (6.1)	66 (6.3)
Desflurane	105 (5.1)	81 (5.0)	73 (10.3)	70 (8.9)
Sevoflurane	108 (5.4)	93 (4.1)	80 (7.5)	68 (10.5)
CO (ml min^{-1})		(%)	(%)	(%)
Enflurane	247 (16)	103 (6.9)	92 (8.5)	64 (5.1)
Isoflurane	238 (16)	103 (1.0)	10 0 (2.7)	97 (8.2)
Desflurane	236 (21)	103 (5.4)	98 (7.8)	10 2 (5.6)
Sevoflurane	273 (23)	95 (3 8)	93 (5 7)	90 (5.9)
d*P*/d*t*max (mm Hg s^{-1})		(%)	(%)	(%)
Enflurane	473 0 (685)	87 (8.7)	60 (12.2)	28 (3.7)
Isoflurane	475 8 (423)	10 1 (5.4)	85 (8 1)	56 (9.6)
Desflurane	505 3 (583)	88 (6.0)	66 (11.8)	57 (11.7)
Sevoflurane	524 6 (411)	90 (6.5)	71 (10.6)	48 (12.6)
SVR (mm Hg min $litre^{-1}$)		(%)	(%)	(%)
Enflurane	396 (11)	82 (2.8)	68 (4.6)	56 (3.5)
Isoflurane	406 (30)	95 (3.3)	83 (6.4)	58 (6.6)
Desflurane	400 (28)	84 (3.3)	64 (9.4)	56 (7.7)
Sevoflurane	362 (36)	95 (2.7)	78 (6.8)	62 (10.9)

rane group, *n*=10; desflurane group, *n*=10; inhalation anaesthetic without coronary occlusion, *n*=8).

HAEMODYNAMIC FUNCTION

Effects of inhalation anaesthetics on normal myocardium

In eight rabbits, the effect of the inhalation anaesthetic on normal myocardium was tested in the experimental model of the present study (table 1). Two to three different anaesthetics were tested in each animal. There was a similar decrease in LVPSP, d*P*/d*t*max and SVR in all groups at 1.5 MAC. CO was maintained at lower concentrations until 1.0 MAC (the concentration used in the ischaemia–reperfusion experiments), but decreased at 1.5 MAC of enflurane.

Ischaemia–reperfusion experiments

The haemodynamic variables are summarized in figures 1 and 2 and table 2. During baseline recordings, groups were comparable in LVPSP and CO. By chance, heart rate was higher in the isoflurane, sevoflurane and desflurane groups compared with the control group (figs 1, 2). Consequently, RPP, as a major determinant of myocardial oxygen consumption, was comparable between the control group and the enflurane group and was higher in the isoflurane, sevoflurane and desflurane groups during baseline conditions.

In all groups, coronary occlusion was accompanied by a small reduction in LVPSP (15%), d*P*/d*t*max (23%) and CO (20%) (table 2; figs 1, 2). SVR remained unchanged. Diastolic function showed a prolongation of the time constant of decrease in isovolumic LV pressure (τ increased by 20%) and an increase in LVEDP (42%) during coronary artery occlusion (table 2) (all values at 25 min of coronary artery occlusion).

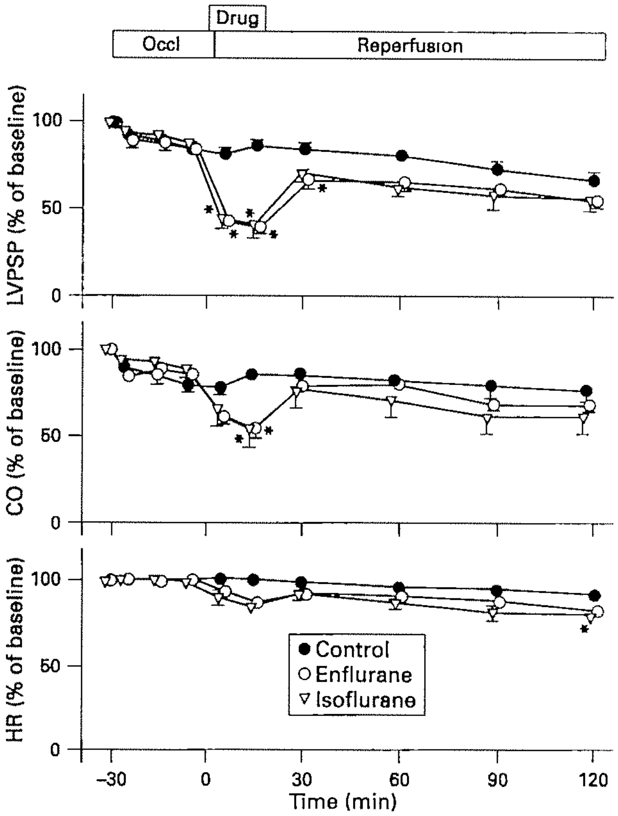

Figure 1 Line plot showing the time course of left ventricular peak systolic pressure (LVPSP), cardiac output (CO) and heart rate (HR) during experiments in the control, enflurane and isoflurane groups. Data are percentage changes (SEM) from baseline. Baseline LVPSP was 101 (SEM 5) mm Hg in the control group, 104 (6) mm Hg in the enflurane group and 118 (3) mm Hg in the isoflurane group. Baseline CO was 265 (20) ml min^{-1} in the control group, 285 (16) ml min^{-1} in the enflurane group and 286 (11) ml min^{-1} in the isoflurane group. Baseline HR was 239 (11) beat min^{-1} in the control group, 252 (6) beat min^{-1} in the enflurane group and 290 (5) beat min^{-1} in the isoflurane group. Occl.=Time of coronary occlusion; Drug=time of anaesthetic administration *$P<0.05$ *vs* control group.

During the reperfusion period, the reduction in LVPSP (to 87% of baseline) and CO (to 85% of baseline) at 15 min of reperfusion remained unchanged in the untreated controls. Administration of 1.0 MAC of the volatile anaesthetics during the first 15 min of reperfusion caused a further decline in LVPSP to 39–54% of baseline values (all $P<0.05$ compared with the control group). Simultaneously, CO decreased in the enflurane group (54% of baseline values) and in the isoflurane group (53% of baseline values) (both $P<0.05$ compared with the control group). In the sevoflurane and desflurane groups, CO was reduced to a much smaller extent and was not significantly different from the control group (sevoflurane group 67% ($P=0.39$); desflurane group 79% of baseline values ($P=0.98$)). SVR was reduced in all treatment groups. With regard to diastolic function during reperfusion, the time constant of decrease in isovolumic LV pressure remained prolonged to the same extent as during the occlusion period in the control group, while administration of the inhalation anaesthetics further prolonged τ. At 15 min of reperfusion, d*P*/d*t*min was reduced significantly in all treatment groups, while there were no differences in LVEDP between treatment and control groups.

After discontinuation of the volatile anaesthetics,

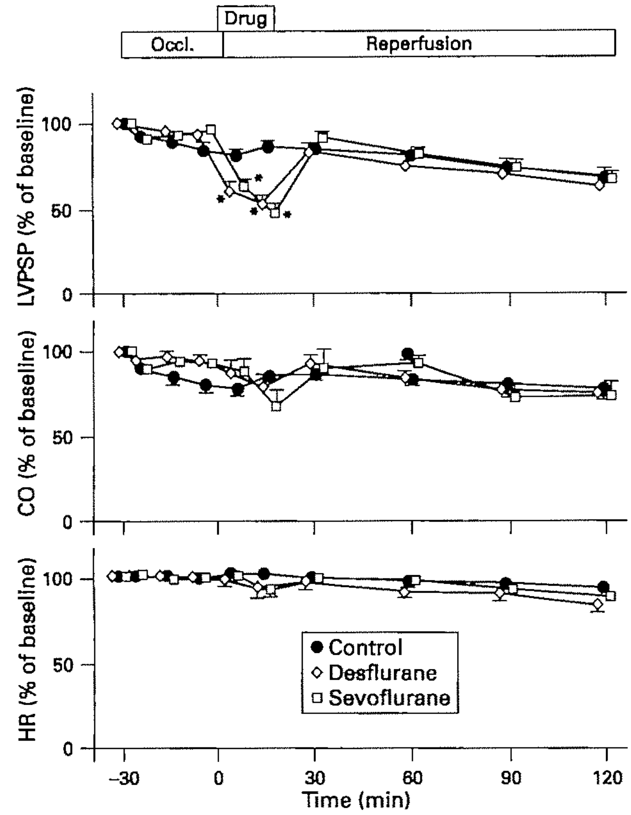

Figure 2 Line plot showing the time course of left ventricular peak systolic pressure (LVPSP), cardiac output (CO) and heart rate (HR) during experiments in the control, sevoflurane and desflurane groups. Data are percentage changes (SEM) from baseline. Baseline LVPSP was 115 (3) mm Hg in the sevoflurane group and 111 (2) mm Hg in the desflurane group (each n=10). Baseline CO was 269 (14) ml min^{-1} in the sevoflurane group and 275 (13) ml min^{-1} in the desflurane group. Baseline HR was 279 (7) beat min^{-1} in the sevoflurane group and 286 (7) beat min^{-1} in the desflurane group Occl.=Time of coronary occlusion; Drug=time of anaesthetic administration. *$P<0.05$ *vs* control group.

haemodynamic variables recovered to values not different from controls, except for enflurane-treated animals, which had a lower LVPSP at 30 min of reperfusion (fig. 1).

After 120 min of reperfusion, LVPSP was reduced by approximately 35% of baseline in all groups and d*P*/d*t*max was reduced by 35–59% of baseline values at the end of the reperfusion period, still reflecting impaired myocardial function in all groups at the end of the experiments. Heart rate after 120 min of reperfusion was reduced by 8% of baseline values in the control group and by approximately 15% in the treatment groups, with no significant differences compared with controls except for the isoflurane group, in which heart rate was reduced by 20% of baseline ($P<0.05$). As a consequence of the reduction in heart rate and LVPSP, RPP was reduced by 36–50%, with no significant differences between the control and treatment groups. τ was prolonged to a greater extent in the enflurane group ($P<0.05$), while simultaneously, LVEDP increased by 75% in this group (P=0.06 compared with the control group).

INFARCT SIZE

Mean LV weight was 5.12 (0.13) g, with no differences between groups (data from individual groups are given in table 3). The ischaemic–reperfused area (area at risk) constituted 30.9 (1.1)% of LV. In the control group, infarct size was 48.8 (4.7)% of the area at risk (fig. 3). Infarct size was markedly reduced in the desflurane group (32.5 (3.3)% of the area at risk; P=0.021 *vs* control) and in the sevoflurane group (35.9 (1.9)%; P=0.097 *vs* control). In the enflurane-treated animals, infarct size was 38.7 (4.9)% (P=0.272 *vs* control). Isoflurane did not influence infarct size (47.5 (4.8)%; P=1.000 *vs* control). The relationship between the area at risk size and the amount of infarcted tissue is shown in figure 4. The slope of the regression line relating infarct size and area at risk size was markedly reduced in the sevoflurane (0.24 (0.10)) and desflurane (0.39 (0.18)) groups compared with the control group (0.78 (0.11)). In enflurane-treated hearts, the slope was 0.65 (0.15), and in isoflurane treated hearts it was 0.74 (0.20). Analysis of variance of multiple regressions followed by analysis of covariance showed no significant differences between groups (P=0.139).

Discussion

The main finding of our study was that inhalation of desflurane and sevoflurane during the first 15 min of reperfusion reduced infarct size after regional myocardial ischaemia in the rabbit heart *in vivo*. Enflurane offered only marginal protective effects and isoflurane had no effect on infarct size. Haemodynamic changes during reperfusion were smaller during administration of sevoflurane and desflurane compared with inhalation of enflurane or isoflurane.

CRITIQUE OF METHODS

Eight animals in the control group came from a previous study.[4] Infarct size in the *in situ* rabbit heart has been shown to vary over a wide range.[16 17] Control groups between studies should only be compared with each other if experimental conditions such as duration of coronary artery occlusion, pericardial temperature and anaesthetic regimens are similar, because all of these conditions may influence infarct size in rabbits.[18–20] We used chloralose for basal anaesthesia because it maintains near normal cardiovascular reflexes accompanied by a high sympathetic tone.[21] There are no studies investigating infarct size in rabbits using chloralose anaesthesia and the same duration of ischaemia and reperfusion. To prevent an increase in type I error by repeated use of the same controls, the two treatment groups of the previous study were included in the statistical evaluation. Therefore, the use of eight animals from a previous control group should not have produced false positive results. Group size was greater in this study than in our previous study because more animals were necessary to detect differences between groups if seven groups were studied.

To exclude the influence of the area at risk size on infarct size,[22] we analysed the relationship between the mass of the area at risk and infarct mass. From figure 4 it is apparent that desflurane and sevoflurane reduced the slope of the regression line compared with the control group, indicating myocardial protective actions on reperfusion injury. However, analysis

Table 2 Haemodynamic variables during ischaemia–reperfusion experiments. Data are mean (SEM). LVEDP = Left ventricular end-diastolic pressure; d*P*/d*t*max = maximum rate of left ventricular pressure increase; SVR = systemic vascular resistance; RPP = rate pressure product; τ = time constant of decrease in isovolumic left ventricular pressure. *$P<0.05$ compared with control group; †$P<0.05$ compared with baseline conditions

		Coronary occlusion		Reperfusion			
	Baseline	5 min	25 min	5 min	15 min	30 min	120 min
LVEDP (mm Hg)		(%)	(%)	(%)	(%)	(%)	(%)
Control	7.7 (0.7)	145 (9)	142 (8)	148 (11)	146 (8)	134 (8)	107 (15)
Enflurane	7.7 (0.9)	169 (33)	149 (22)	131 (11)	137 (13)	142 (11)	175 (29)
Isoflurane	6.1 (0.5)	162 (12)	179 (17)	147 (8)	152 (15)	165 (19)	143 (14)
Desflurane	5.9 (0.5)	137 (9)	112 (18)	139 (12)	127 (10)	120 (10)	113 (7)
Sevoflurane	6.5 (0.5)	127 (8)	137 (10)	131 (9)	129 (9)	136 (9)	121 (8)
d*P*/d*t*max (mm Hg s^{-1})		(%)	(%)	(%)	(%)	(%)	
Control	4788 (353)	84 (3)	78 (6)	66 (3)†	72 (3)	70 (2)†	56 (7)†
Enflurane	5308 (334)	80 (4)	75 (5)†	29 (3)*†	26 (3)*†	51 (6)†	39 (4)†
Isoflurane	6341 (351)	93 (4)	86 (7)	32 (7)* †	29 (5)*†	58 (8)†	42 (9)†
Desflurane	5240 (267)	95 (3)	95 (5)	48 (5)†	41 (4)*†	73 (6)†	49 (5)†
Sevoflurane	5509 (219)	88 (6)	95 (3)	51 (6)†	37 (6)*†	84 (7)	53 (4)†
SVR (mm Hg min litre^{-1})		(%)	(%)	(%)	(%)	(%)	
Control	336 (31)	105 (3)	99 (4)	99 (3)	96 (3)	94 (3)	79 (7)
Enflurane	306 (20)	104 (8)	98 (14)	48 (8)*†	40 (6)*†	71 (12)	54 (10)†
Isoflurane	374 (16)	103 (4)	100 (4)	45 (4)* †	45 (6)*†	78 (5)	57 (9)†
Desflurane	365 (27)	102 (3)	97 (4)	51 (4)*	46 (4)*	81 (4)	68 (6)
Sevoflurane	394 (19)	103 (6)	105 (3)	57 (3)*	49 (5)*	62 (3)	96 (23)
RPP (mm Hg min^{-1} 10^3)		(%)	(%)	(%)	(%)	(%)	
Control	24.5 (2.2)	92 (2)	84 (6)	82 (4)	87 (4)	83 (4)	63 (7)†
Enflurane	26.4 (1.7)	91 (5)	98 (14)	48 (8)*†	39 (6)*†	71 (12) †	55 (10)†
Isoflurane	35.1 (0.9)	93 (2)*	97 (11)	45 (7)*†	37 (6)*†	71 (8)†	50 (7)†
Desflurane	31.8 (1.2)	96 (2)*	98 (8)	66 (11)†	56 (9)*†	86 (11)	56 (8)†
Sevoflurane	32.0 (1.2)	92 (4)*	96 (3)	64 (7)†	46 (7)*†	89 (5)	61 (7)†
τ (ms)		(%)	(%)	(%)	(%)	(%)	
Control	16.4 (1.6)	118 (6)	120 (7)	122 (8)	121 (5)	115 (4)	138 (15)†
Enflurane	15.2 (0.8)	128 (9)	124 (6)	227 (46)*†	197 (22)†	159 (25)	191 (1 2)*†
Isoflurane	12.4 (0.5)	123 (4)	140 (18)	204 (31)†	244 (35)*†	134 (15)	160 (12)†
Desflurane	12.6 (0.5)	118 (6)	118 (6)	140 (15)	160 (20)†	123 (10)	151 (8)†
Sevoflurane	13.6 (0.7)	124 (8)	115 (5)	136 (12)	231 (48)*†	104 (5)	137 (9)†

Table 3 Weights and area at risk size. Data are mean (SEM). LV = Left ventricle

	Control	Enflurane	Isoflurane	Sevoflurane	Desflurane
Body weight (kg)	3.69 (0.08)	3.50 (0.12)	3.65 (0.09)	3.43 (0.07)	3.89 (0.18)
LV weight (g)	5.23 (0.36)	4.97 (0.31)	5.15 (0.36)	4.67 (0.34)	4.99 (0.26)
Area at risk (g)	1.66 (0.17)	1.51 (0.15)	1.50 (0.12)	1.45 (0.10)	1.32 (0.11)
Area at risk /LV (%)	32.9 (3.34)	28.9 (2.02)	31.1 (2.22)	35.8 (2.32)	29.3 (1.74)
Infarct size (g)	0.85 (0.14)	0.62 (0.12)	0.76 (0.10)	0.52 (0.04)	0.43 (0.07)

of variance for differences between regression slopes did not confirm this as statistically significant with seven experimental groups.

Heart rate, and consequently RPP, were higher in the isoflurane, desflurane and sevoflurane groups compared with the control group during baseline measurements. Because d*P*/d*t* and τ are influenced by HR, comparison of these variables between groups is difficult. However, differences in HR should not be responsible for the reduction in infarct size in the sevoflurane and desflurane groups, because bradycardia but not tachycardia has been demonstrated to offer beneficial effects against myocardial ischaemia–reperfusion injury.[23,24]

INTERPRETATION OF RESULTS

Coronary artery reperfusion has become the treatment of choice in myocardial infarction. While there is no question that timely restoration of coronary blood flow is essential for the salvage of ischaemic myocardium, reperfusion of ischaemic myocardium after temporary coronary artery occlusion can initiate structural and biochemical changes that limit the amount of potentially salvageable myocardium (reperfusion injury).[1] The cause of this injury is apparently multifactorial.

A protective effect of inhalation anaesthetics on ischaemic–reperfused myocardium may be caused by negative inotropic and chronotropic actions. The inhalation anaesthetics, halothane, enflurane and isoflurane, have been shown to depress myocardial contractility in a dose-dependent manner. Under aerobic conditions, isoflurane may depress myocardial contractility less than halothane or enflurane[25,26] and halothane exerts most pronounced negative inotropic actions during post-ischaemic periods.[27] For the new anaesthetics, *in vivo* studies showed comparable cardiovascular effects of sevoflurane and isoflurane.[28–30] Desflurane had similar haemodynamic effects as isoflurane in patients with coronary artery disease, except for an increase in pulmonary artery pressure and pulmonary capillary wedge pressure.[31] In reperfused isolated rat hearts, the effects of isoflurane, enflurane and sevoflurane on cardiovascular haemodynamics were similar.[27] The aim of our study

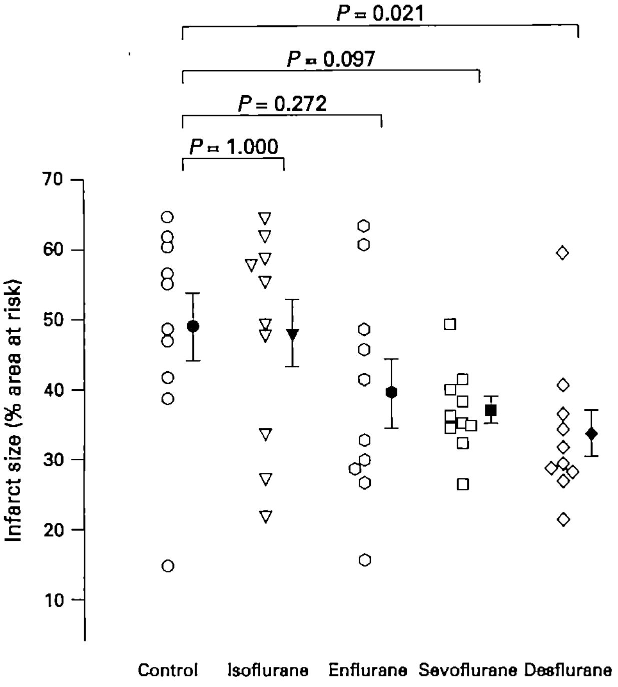

Figure 3 Infarct size as a percentage of the area at risk in the control, isoflurane, enflurane, sevoflurane and desflurane groups. Open symbols=single data points, filled symbols=mean (SEM).

was to investigate the effects of volatile anaesthetics on reperfusion injury *in vivo*. To exclude effects of volatile anaesthetics on the severity of ischaemia, we used α-chloralose for baseline anaesthesia and the volatile anaesthetics were administered only during early reperfusion to investigate specific actions against reperfusion injury. However, it is possible that alterations of systemic haemodynamics during the first 15 min of reperfusion also had effects on infarct size. Left ventricular unloading and a reduction in myocardial oxygen demand have been associated with beneficial effects against myocardial reperfusion injury.[32] LVPSP was reduced in all treatment groups, but was most pronounced in the enflurane and isoflurane groups. RPP is a variable of myocardial energy demand and oxygen consumption.[33] In our study, RPP decreased to a greater extent in the enflurane and isoflurane groups than in animals treated with sevoflurane or desflurane. However, reduction in infarct size in our study was greater using sevoflurane or desflurane than in animals which received enflurane or isoflurane. In the same experimental set-up, halothane offered pronounced protective effects against reperfusion injury even if the haemodynamic side effects were balanced by concomitantly infused norepinephrine (noradrenaline).[4]

It cannot be completely ruled out that favourable changes in myocardial inotropy and myocardial oxygen supply and demand relations during the first 15 min of reperfusion have contributed to protective effects against reperfusion injury. However, it is unlikely that they are solely responsible for the beneficial actions of sevoflurane and desflurane in this setting, and this supports the hypothesis that volatile anaesthetics also cause myocardial protection *via* other mechanisms. In isolated rat hearts perfused in a Langendorff mode, an experimental set-up where changes in haemodynamics play only a minor role, rapid recovery of post-ischaemic function was observed in desflurane-treated hearts.[8 9] After treatment with the other volatile anaesthetics, the hearts showed slower recovery of myocardial function, although all anaesthetics improved myocardial function after 60 min of reperfusion compared with control hearts.

With regard to lethal cellular injury, determined by creatine kinase release, these experiments showed that isoflurane had no effect on early lethal cellular injury compared with controls.[8 9] This is in accordance with our experiments *in vivo*, which showed no reduction in infarct size in isoflurane-treated animals compared with the control group. An increase in creatine kinase release after discontinuation of sevoflurane was observed in isolated rat hearts.[8 9] *In vivo*, there was a marked reduction in infarct size after inhalation of sevoflurane. These differences may suggest differences in early and late protection

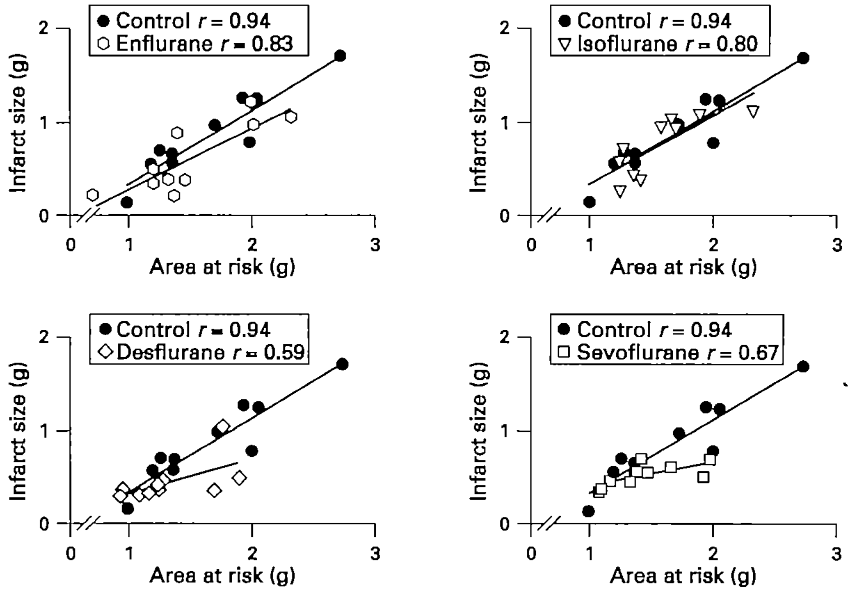

Figure 4 Scatterplot of the relationship between infarct size and size of the area at risk. Slopes of regression lines were smaller in the sevoflurane and desflurane groups compared with the control group. Control group, y=0.78 (SEM 0.11) x–0.44 (0.19), sevoflurane group, y=0.24 (0.10) x–0.17 (0.14); desflurane group, y=0.39 (0.18) x–0.09 (0.25); enflurane group, y=0.65 (0.15) x–0.37 (0.24); isoflurane group, y=0.74 (0.20) x–0.39 (0.31).

against myocardial reperfusion injury by volatile anaesthetics.

Inhalation of anaesthetic was started 3 min before the end of coronary artery occlusion to ensure that a stable concentration of the anaesthetic was achieved at the start of reperfusion. Takahata, Ichihara and Ogawa demonstrated that sevoflurane attenuated ischaemic myocardial injury, an anti-ischaemic effect that could not be explained solely in terms of the haemodynamic actions of sevoflurane.[34] Isoflurane has been shown to exert protective effects if applied during ischaemia and reperfusion, despite maintenance of heart rate and arterial pressure at control values.[35] Because the rabbit has virtually no collateral circulation[36] and the volatile anaesthetics were administered for only 3 min during ischaemia, it is unlikely that a potential anti-ischaemic effect of volatile anaesthetics contributed to differences in infarct size. Volatile anaesthetics were titrated to achieve an end-tidal concentration corresponding to 1.0 MAC for rabbits. In clinical situations, comparison of volatile anaesthetics is performed using MAC values. Although the inhalation anaesthetics were administered 3 min before reperfusion, it is possible that steady state myocardial tissue concentrations had not been achieved. Differences in myocardial tissue concentrations during the early reperfusion period could not be excluded. However, the most lipophilic substance (halothane) and the least lipophilic substance (sevoflurane) caused similar reductions in infarct size.[4]

Apart from effects on systemic haemodynamics, other mechanisms have been proposed to offer potential protective effects against reperfusion injury. Beneficial alterations in intracellular calcium homeostasis,[37] actions on activated leucocytes and effects on oxygen-derived free radicals can attenuate reperfusion injury.[38] Volatile anaesthetics have been shown to influence, at least in part, sarcoplasmic reticulum function[39–41] and adhesion of leucocytes in the coronary system.[42] The protective effect of sevoflurane and desflurane observed in our study might be caused in part by actions on these cellular mechanisms. However, the exact mechanism of protection cannot be determined in the model used.

Because of increasing clinical use of thrombolysis, percutaneous balloon angioplasty and coronary bypass surgery, it is of great practical interest to determine if additional therapeutic intervention during the ischaemia–reperfusion period can lead to a reduction in ischaemia–reperfusion injury. Accumulated experimental evidence from *in vitro* and *in vivo* studies for protective effects of volatile anaesthetics should lead to clinical studies investigating effects of volatile anaesthetics on myocardial reperfusion injury.

In summary, we have shown that inhalation of sevoflurane and desflurane during the early reperfusion period reduced myocardial reperfusion injury after coronary artery occlusion *in vivo*, while enflurane showed only marginal protective effects and isoflurane offered no protection. In addition, the two new volatile anaesthetics altered systemic haemodynamics less than isoflurane and enflurane.

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References

1. Jennings RB, Yellon DM. Reperfusion injury. Definitions and historical background. In: Yellon DM, Jennings RB, eds. *Myocardial Protection: The Pathophysiology of Reperfusion and Reperfusion Injury.* New York: Raven Press, 1992; 1–11.
2. Siegmund B, Schlack W, Ladilov YV, Balser C, Piper HM. Halothane protects cardiomyocytes against reoxygenation-induced hypercontracture. *Circulation* 1997; **96**: 4372–4379.
3. Schlack W, Hollmann M, Stunneck J, Thämer V. Effect of halothane on myocardial reoxygenation injury in the isolated rat heart. *British Journal of Anaesthesia* 1996; **76**: 860–867.
4. Schlack W, Preckel B, Barthel H, Obal D, Thämer V. Halothane reduces reperfusion injury after regional ischaemia in the rabbit heart *in vivo*. *British Journal of Anaesthesia* 1997, **79**: 88–96.
5. Sahlman L, Waagstein L, Haljamae H, Ricksten SE. Protective effects of halothane but not isoflurane against global ischaemic injury in the isolated working rat heart. *Acta Anaesthesiologica Scandinavica* 1995, **39**: 312–316.
6. Marijic J, Stowe DF, Turner LA, Kampine JP, Bosnjak ZJ. Differential protective effects of halothane and isoflurane against hypoxic and reoxygenation injury in the isolated guinea pig heart. *Anesthesiology* 1990; **73**: 976–983.
7. van Ackern K, Vetter HO, Bruckner UB, Madler C, Mittman U, Peter K. Effects of enflurane on myocardial ischaemia in the dog. *British Journal of Anaesthesia* 1985; **57**: 497–504.
8. Schlack W, Preckel B, Stunneck D, Thämer V. Different inhalational anaesthetics have different protective effects against the reperfusion injury of the heart. *British Journal of Anaesthesia* 1997; **78** (Suppl. 1): A.150, 45–46.
9. Schlack W, Preckel B, Stunneck D, Thämer V. Effects of halothane, enflurane, isoflurane, sevoflurane and desflurane on myocardial reperfusion injury in the isolated rat heart. *British Journal of Anaesthesia* 1998; **81**: 913–919.
10. Drummond JC. MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit. And a test for the validity of MAC determination. *Anesthesiology* 1985; **62**: 336–338.
11. Scheller MS, Saidman LJ, Partridge BL. MAC of sevoflurane in humans and the New Zealand white rabbit. *Canadian Journal of Anaesthesia* 1988; **35**: 153–156.
12. Doorley BM, Waters SJ, Terrell RC, Robinson JL. MAC of I-653 in beagle dogs and New Zealand white rabbits. *Anesthesiology* 1988; **69**: 89–91.
13. Abel FL. Maximal negative dP/dt as an indicator of end of systole. *American Journal of Physiology* 1981, **240**: H676–H679.
14. Brutsaert DL, Rademakers FE, Sys SU, Gillebert TC, Housmans PR. Analysis of relaxation in the evaluation of ventricular function of the heart. *Progress in Cardiovascular Diseases* 1985; **28**: 143–163.
15. Armitage P, Berry G. *Statistical Methods in Medical Research.* Oxford. Blackwell Scientific, 1987, 282–310.
16. Williams MW, Taft CS, Ramnauth S, Zhao ZQ, Vinten-Johansen J. Endogenous nitric oxide (NO) protects against ischaemia–reperfusion injury in the rabbit. *Cardiovascular Research* 1995; **30**: 79–86.
17. Hale SL, Hammerman H, Kloner RA. Effect of two perfluorocarbon emulsions on reperfusion injury after coronary artery occlusion in rabbits. *Basic Research in Cardiology* 1995, **90**: 404–409.
18. Walker MJA, Curtis MJ, Hearse DJ, Campbell RWF, Janse MJ, Yellon DM, Cobbe SM, Coker SJ, Harness JB, Harron DWG, Higgins AJ, Julian DG, Lab MJ, Manning AS, Northover BJ, Parratt JR, Riemersma RA, Riva E, Russell DC, Sheridan DJ, Winslow E, Woodward B. The Lambeth Conventions: guidelines for the study of arrhythmias in ischaemia, infarction and reperfusion. *Cardiovascular Research* 1988; **22**: 447–455.
19. Chien GL, Wolff RA, Davis RF, Van Winkle DM. "Normothermic range" temperature affects myocardial infarct size. *Cardiovascular Research* 1994, **28**: 1014–1017.
20. Chakrabarty S, Thomas P, Sheridan DJ. Arrhythmias, haemodynamic changes and extent of myocardial damage during coronary ligation in rabbits anaesthetized with halothane, alpha chloralose or pentobarbitone. *International Journal of Cardiology* 1991, **31**: 9–14.
21. Armstrong GG, Porter H, Langston JB. Alteration of carotid occlusion response by anesthesia. *American Journal of Physiology* 1961; **201**: 897–900.
22. Ytrehus K, Liu Y, Tsuchida A, Miura T, Liu GS, Yang XM, Herbert D, Cohen MV, Downey JM. Rat and rabbit heart infarction: effects of anesthesia, perfusate, risk zone, and

method of infarct sizing. *American Journal of Physiology* 1994; **267**: H2383–H2390.

23. Schlack W, Ebel D, Grunert S, Halilovic S, Meyer O, Thämer V. Effect of heart rate reduction by 4-(N-ethyl-N-phenyl-amino)-1,2-dimethyl-6-(methylamino)pyrimidinium chloride on infarct size in dog. *Drug Research* 1998; **48**: 26–33.
24. Redwood DR, Smith ER, Epstein SE. Coronary artery occlusion in conscious dog. Effects of alterations in heart rate and arterial pressure on the degree of myocardial ischemia. *Circulation* 1972; **46**: 323–332.
25. Stowe DF, Marijic J, Bosnjak ZJ, Kampine JP. Direct comparative effects of halothane, enflurane, and isoflurane on oxygen supply and demand in isolated hearts. *Anesthesiology* 1991; **74**: 1087–1095.
26. Sahlman L, Henriksson BA, Martner J, Ricksten SE. Effects of halothane, enflurane, and isoflurane on coronary vascular tone, myocardial performance, and oxygen consumption during controlled changes in aortic and left atrial pressure. *Anesthesiology* 1988; **69**: 1–10.
27. Oguchi T, Kashimoto S, Yamaguchi T, Nakamura T, Kumazawa T. Comparative effects of halothane, enflurane, isoflurane, and sevoflurane on function and metabolism in the ischaemic rat heart. *British Journal of Anaesthesia* 1995; **74**: 569–575.
28. Kazama T, Ikeda K. The comparative cardiovascular effects of sevoflurane with halothane and isoflurane. *Journal of Anaesthesia* 1988; **2**: 63–68.
29. Bernard JM, Wouters PF, Doursout MF, Florence B, Chelly JE, Merin RG. Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. *Anesthesiology* 1990; **72**: 659–662.
30. Conzen PF, Vollmar B, Habazettl H, Frink EJ, Peter K, Messmer K. Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. *Anesthesia and Analgesia* 1992; **74**: 79–88.
31. Grundmann U, Müller M, Kleinschmidt S, Larsen B, Larsen R. Cardiovascular effects of desflurane and isoflurane in patients with coronary artery disease. *Acta Anaesthesiologica Scandinavica* 1996; **40**: 1101–1107.
32. Laschinger JC, Grossi EA, Cunningham JN jr, Krieger KH, Baumann FG, Colvin SB, Spencer FC. Adjunctive left ventricular unloading during myocardial reperfusion plays a major role in minimizing myocardial infarct size. *Journal of Thoracic and Cardiovascular Surgery* 1985; **90**: 80–85.
33. Neely JR, Liebermeister H, Battersby EJ, Morgan HE. Effect of pressure development on oxygen consumption by isolated rat heart. *American Journal of Physiology* 1967; **212**: 804–814.
34. Takahata O, Ichihara K, Ogawa H. Effects of sevoflurane on ischaemic myocardium in dogs. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 449–456.
35. Kanaya N, Kobayashi I, Nakayama M, Fujita S, Namiki A. ATP sparing effect of isoflurane during ischaemia and reperfusion of the canine heart. *British Journal of Anaesthesia* 1995; **74**: 563–568.
36. Maxwell MP, Hearse DJ, Yellon DM. Species variations in the coronary circulation during regional myocardial ischaemia: a critical determinant of the rate of evolution and extent of myocardial infarction. *Cardiovascular Research* 1987; **21**: 737–746.
37. Siegmund B, Schlüter KD, Piper HM. Calcium and the oxygen paradox. *Cardiovascular Research* 1993; **27**: 1778–1783.
38. Mullane KM, Young M. The contribution of neutrophil activation and changes in endothelial function to myocardial ischemia–reperfusion injury. In: Yellon DM, Jennings RB, eds. *The Pathophysiology of Reperfusion and Reperfusion injury*. New York: Raven Press, 1992; 59–83.
39. Lynch C III, Frazer MJ. Anaesthetic alterations of ryanodine binding by cardiac calcium release channels. *Biochimica et Biophysica Acta* 1994; **1194**: 109–117.
40. Lynch C III. Differential depression of myocardial contractility by halothane and isoflurane in vitro. *Anesthesiology* 1986; **64**: 620–631.
41 Blanck TJJ, Thompson M. Enflurane and isoflurane stimulate calcium transport by cardiac sarcoplasmic reticulum. *Anesthesia and Analgesia* 1982; **61**: 142–145.
42. Kowalski C, Zahler S, Becker BF, Flaucher A, Conzen PF, Gerlach E, Peter K. Halothane, isoflurane, and sevoflurane reduce postischemic adhesion of neutrophils in the coronary system. *Anesthesiology* 1997; **86**: 188–195.

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Effects of halothane, enflurane, isoflurane, sevoflurane and desflurane on myocardial reperfusion injury in the isolated rat heart

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Summary

A specific action against myocardial reperfusion injury of the oxygen paradox type was recently characterized for halothane after anoxic perfusion in isolated rat hearts and isolated cardiomyocytes. In this study, we have characterized the protective effects of the clinically available inhalation anaesthetics during reperfusion after ischaemia. In isolated, isovolumically beating rat hearts perfused at a constant flow (10 ml min^{-1}, P_{O_2} 80 kPa) and paced at 350 beat min^{-1}, we determined left ventricular developed pressure (LVDP) and release of creatine kinase (CKR) as indices of myocardial performance and cellular injury, respectively. Seven control hearts underwent 30 min of no-flow ischaemia and 1 h of reperfusion. In the treatment groups, halothane, enflurane, isoflurane, sevoflurane or desflurane (each group n=6) was added to the perfusion medium for the first 30 min of reperfusion at a concentration corresponding to 1.5 MAC in the rat. In the control group, cellular injury occurred at early reperfusion (peak CKR 283 (SEM 57) iu $litre^{-1}$ at 10 min of reperfusion). Peak CKR to the coronary venous effluent was attenuated by all anaesthetics (halothane group 156 (45), enflurane group 134 (20), sevoflurane group 132 (20), desflurane group 159 (25) iu $litre^{-1}$; each P<0.05). Isoflurane did not differ from controls (303 (53) iu $litre^{-1}$; P=0.5). In the sevoflurane group, there was a delayed peak CKR after discontinuation of the anaesthetic at 30 min of reperfusion (260 (34) iu $litre^{-1}$). Functional recovery was improved by all anaesthetics, but was seen much earlier with desflurane (LVDP 28 (3)% of baseline at 5 min reperfusion compared with halothane (6 (1)%), enflurane (11 (3)%), isoflurane (9 (6)%), sevoflurane (10(2)%) and controls (3 (1)% of baseline)). At 30 min of reperfusion, recovery of LVDP was improved to a similar extent by all anaesthetics (halothane 30 (9)%, enflurane 36 (9)%, isoflurane 33 (5)%, sevoflurane 30 (5)%, desflurane 36 (4)% of baseline values) compared with controls (13 (5)%; each P<0.05). All inhalation anaesthetics protected against myocardial reperfusion injury, but showed differences in attenuation of cellular injury and functional recovery. These differences may suggest different protective mechanisms. (*Br. J. Anaesth.* 1998; **81**: 913–919).

Keywords: anaesthetics volatile, halothane; anaesthetics volatile, enflurane; anaesthetics volatile, isoflurane; anaesthetics volatile, sevoflurane, anaesthetics volatile, desflurane; heart, myocardial function, model, heart; rat

It was reported recently that cardioprotection by halothane in isolated anoxic–reoxygenated rat hearts was much more pronounced if the substance was administered after the period of anoxic perfusion (during reoxygenation) than if given during the anoxic period itself.[1] From these findings it was concluded that, apart from displaying anti-ischaemic effects, halothane may have a specific effect on reperfusion injury. This protective effect was also confirmed *in vivo* in a rabbit model of coronary artery occlusion and subsequent reperfusion.[2] One MAC of halothane given during the initial 15 min of reperfusion caused a 38% reduction in infarct size, even if the haemodynamic effects were counteracted by i.v. norepinephrine (noradrenaline). Using the model of anoxic–reoxygenated isolated cardiomyocytes, it was possible to confirm a protective effect against reperfusion injury of the "oxygen paradox" type and to study the underlying protective mechanism.[3–5] Halothane 1.5 MAC given during reoxygenation prevented reoxygenation-induced intracellular Ca^{2+} oscillations which are responsible for cellular hypercontracture and cell death at early reperfusion.[6] Therefore, the above cited studies strongly suggest a specific protective mechanism of halothane against reperfusion injury in the heart.

We hypothesized that other inhalation anaesthetics may have similar effects on the ischaemic–reperfused myocardium. Therefore, the aim of this study was to describe the effects of the currently available inhalation anaesthetics, halothane, enflurane, isoflurane, sevoflurane and desflurane, on myocardial reperfusion injury after ischaemia. We used an isolated rat heart model with 30 min of no-flow ischaemia and 1 h of reperfusion and supplied the inhalation anaesthetics for the first 30 min of reperfusion. In this model, extrinsic humoral and autonomic nervous system influences were excluded and ventricular volume, coronary flow and heart rate were kept constant.

Materials and methods

The study was performed in accordance with the regulations of the German Law for the Protection of Animals and local institutional regulations.

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EXPERIMENTAL PREPARATION

Hearts from male Wistar rats (weighing 250–300 g), anaesthetized with halothane, were excised rapidly and mounted on a Langendorff perfusion system. Retrograde perfusion was initiated with an oxygenated modified Krebs–Henseleit buffer containing (mmol litre^{-1}): NaCl 116, KCl 4.7, $MgSO_4$ 1.1, KH_2PO_4 1.17, $NaHCO_3$ 24.9, $CaCl_2$ 2.52, glucose 8.3 and pyruvate 2.0; gassed with 95% oxygen–5% carbon dioxide. Flow in the system was controlled by two calibrated roller pumps (Model 7518, Cole-Parmer Instruments, IL, USA). After ligating both venae cavae, the right ventricle was vented via the pulmonary artery with a Teflon catheter (1.2 mm od). Heart rate was maintained at 350 beat min^{-1} by atrial pacing. The stimulation voltage was maintained at 20% above threshold (control 2–4 V) and adjusted continuously throughout the experiment (up to 12 V in reperfused hearts, if necessary). After completion of the experimental preparation, the heart was placed in a water-jacketed chamber at 37°C, filled with humidified, warmed air. The hearts were perfused at a flow rate of 10 ml min^{-1} which was kept constant throughout the perfusion period. During ischaemia, the heart chamber was filled with normal saline to maintain heart temperature at 37°C and gassed with nitrogen to prevent oxygen supply to the ischaemic myocardium by diffusion. In order to ensure the presence of the inhalation anaesthetic with the onset of reperfusion, the hearts were perfused for the last 2 min of the ischaemic period with anoxic buffer equilibrated with 95% nitrogen–5% carbon dioxide containing the different inhalation anaesthetics in the concentrations specified below or buffer alone (controls) at a flow rate of 2 ml min^{-1}. Reperfusion was then initiated by switching back to the initial normoxic perfusion conditions.

For administration of 1.5 MAC of halothane, enflurane and isoflurane, a saturated solution was prepared in the perfusion buffer at 22°C and infused into the perfusion system near the aortic cannula at appropriate fractions of total coronary flow in order to achieve final concentrations of 0.45, 0.96 and 0.47 mmol litre^{-1}, respectively, using a calibrated syringe pump (Model 5003, Precidior Infors, Basel, Switzerland). For the 2-min anoxic perfusion, the saturated solution was prepared in the anoxic buffer. For sevoflurane administration, the saturated solution was prepared using distilled water. During administration of sevoflurane, a more concentrated buffer was used so that the final concentration of solutes was not altered and the final sevoflurane concentration was 0.71 mmol litre^{-1}. Only glass or Teflon tubing was in contact with the perfusion medium containing inhalation anaesthetics. Desflurane was supplied to the perfusion medium using a calibrated vaporizer (Devapor, Dräger Werke, Lübeck, Germany) using a hollow fibre oxygenator (D705 Midflow, DIDECO, Mirandola, Italy) to achieve a perfusate concentration of 1.0 mmol litre^{-1}. Concentrations of the inhalation anaesthetics were determined in the saturated solutions by gas chromatography.

Haemodynamic measurements

For measurements of left ventricular pressure, a latex balloon (size No. 4, Hugo Sachs Elektronik, March, Germany) was introduced into the left ventricle via the cut mitral valve. The balloon was fixed at the tip of a stainless steel cannula (length 5.9 cm) which was connected directly to a pressure transducer (Gould P23, Cleveland, OH, USA). Left ventricular pressure, and (by electronic differentiation) the velocity of the change in left ventricular pressure (d*P*/d*t*) were monitored continuously on an ink recorder (Gould, Mark 260, Cleveland, OH, USA). At the beginning of each experiment, the latex balloon was filled with normal saline (air-bubble free) to achieve an end-diastolic left ventricular pressure of 5 mm Hg. This volume was then held constant for the rest of the experiment. Left ventricular pressure and coronary perfusion pressure signals were digitized at a sampling rate of 2000 Hz using an analogue to digital converter (Data Translation 2801, Marlboro, MA, USA) and then processed on a personal computer system. Left ventricular end-diastole was determined as the point when left ventricular d*P*/d*t* started its rapid upstroke after crossing the zero line. Left ventricular end-systole was defined as the point of minimum d*P*/d*t*.[7] Left ventricular end-diastolic pressure (LVEDP), developed pressure (LVDP), maximum and minimum d*P*/d*t* (d*P*/d*t*max and d*P*/d*t*min) were obtained from the digitized signals. Only hearts with an LVDP greater than 70 mm Hg during the initial control period were used for the study.

Metabolic measurements

Aliquots from the perfusion medium and the coronary venous effluent perfusate were sampled anaerobically at the times indicated. Samples were processed immediately for Po_2 measurements (ABL 30, Radiometer, Copenhagen, Denmark). Oxygen consumption ($\dot{V}o_2$) was calculated according to Fick's principle with the use of Bunsen's solubility coefficient (α'=0.036 μl mm Hg^{-1} ml^{-1}) at 37°C as follows:

$$\dot{V}o_2\ (\mu l\ min^{-1})=(Pa_{O_2}-P\bar{v}_{O_2})\ \alpha'\ CF$$

where Pa_{O_2}=arterial PO_2, $P\bar{v}_{O_2}$=venous PO_2 (kPa) and CF=coronary flow (ml min^{-1}).

For determination of creatine kinase (CK) release, 1-min samples of the effluent were collected at the times indicated (fig. 1). CK activity was measured with an "optimized standard method" according to the recommendations of the Deutsche Gesellschaft für Klinische Chemie (CK test, Boehringer, Mannheim, Germany).

EXPERIMENTAL PROGRAMME

After mounting the heart on the Langendorff apparatus, a preparation and stabilization period of 30 min was allowed. The experimental procedure consisted of three phases: baseline, ischaemia and reperfusion (fig. 1). After a 15-min baseline period with steady state conditions and control measurements of all experimental variables, the hearts underwent 30 min of no-flow ischaemia. After the ischaemic period, the hearts were reperfused with the initial oxygenated medium. The inhalation anaesthetics were added to the perfusion medium to achieve concentrations corresponding to 1.5 rat MAC during the first 30 min of reperfusion starting with a 2-min anoxic wash-in of the agents (each $n=6$). Seven hearts served as controls and underwent the ischaemia–reperfusion programme without intervention. Five hearts received the different inhalation anaesthetics (except halothane) in a randomized order for 5 min during normoxic perfusion conditions for assessment of the haemodynamic effects on normal myocardium in this experimental model. After each agent, 15 min were allowed for full recovery of all haemodynamic variables. The data for halothane on normal myocardium of the rat were taken from a previous study.[1]

DATA ANALYSIS

Data are presented as mean (SEM). The effects of inhalation anaesthetics on normal myocardium were assessed by Student's t test for paired observations. In the ischaemia–reperfusion experiments, statistical analysis was performed using two-way analysis of variance (ANOVA) for time and treatment (experimental group) effects. If an overall significant difference between groups was found, a comparison was performed for each time using one-way ANOVA followed by Dunnetts's post-test when appropriate.

Results

A total of 54 hearts were used. Fourteen hearts did not fulfill the predefined quality criteria (LVDP >70 mm Hg) and were excluded.

HAEMODYNAMIC FUNCTION

Basal values and effects of the inhalation anaesthetics on normal myocardium

In five hearts, enflurane, isoflurane, sevoflurane and desflurane were given in a randomized order at a concentration corresponding to 1.5 MAC (measurements were made after 5 min under steady state conditions and 15 min were allowed for recovery between interventions). Data for halothane (1.5 MAC) were obtained from a previous study with measurements made after 15 min of steady state conditions.[1] During desflurane administration, there was a small initial increase in LVDP and dP/dt of 10–20% before these variables started to decline. This initial increase in contractile force was observed only with desflurane. All inhalation anaesthetics reduced LVDP (halothane to 52%, enflurane to 70%, isoflurane to 65%, sevoflurane to 65% and desflurane to 76% of baseline values, respectively) and dP/dtmax (halothane to 68%, enflurane to 76%, isoflurane to 74%, sevoflurane to 68% and desflurane to 79% of baseline values, respectively). Simultaneously, $\dot{V}o_2$ was reduced (to a similar extent with halothane (to 86%), enflurane (to 75%), isoflurane (to 69%) and sevoflurane (to 76%) but was less pronounced with desflurane (to 90% of baseline)) (table 1).

Table 1 Haemodynamic variables. Effect of the inhalation anaesthetics on normal myocardium. Data are mean (SEM), $n=5$ LVDP=Left ventricular developed pressure; dP/dtmax=maximum velocity of the change in left ventricular pressure, Vo_2=myocardial oxygen consumption. *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with baselines

	Baseline	1.5 MAC
LVDP (mm Hg)		
Halothane	99.3 (1.8)	52.0 (2.7)***
Isoflurane	79.8 (13.5)	51.7 (10.2)**
Enflurane	91.9 (6.9)	64.1 (4.4)***
Sevoflurane	92.6 (5.5)	59.8 (7.0)**
Desflurane	93.5 (8.0)	70.7 (6.6)*
dP/dtmax (mm Hg s^{-1})		
Halothane	3465 (78)	2344 (78)
Isoflurane	2689 (390)	1996 (373)**
Enflurane	3046 (167)	2300 (169)***
Sevoflurane	3014 (124)	2053 (235)**
Desflurane	3172 (153)	2519 (145)**
Vo_2 (μl min^{-1})		
Halothane	896.6 (29.5)	681.0 (21.0)
Isoflurane	159.9 (15.1)	110.6 (12.4)***
Enflurane	151.2 (16.5)	114.6 (18.1)***
Sevoflurane	139.8 (5.7)	107.4 (7.2)***
Desflurane	135.6 (4.4)	122.1 (4.5)**

End-diastolic pressure during ischaemia–reperfusion

During ischaemia, LVEDP increased progressively in all groups from 5.1 (0.3) mm Hg during normoxic baseline conditions to 54.9 (3.0) mm Hg at the end of the ischaemic period, indicating the development of ischaemic contracture. Initiation of anoxic perfusion for wash-in of the inhalation anaesthetics before reperfusion had no effect on LVEDP.

With the onset of reperfusion, all groups showed a further increase in LVEDP (reperfusion contracture, table 2). All inhalation anaesthetics moderately improved overall LVEDP recovery during reperfusion compared with controls ($P<0.05$ each; ANOVA), indicating a reduction in reperfusion contracture. After 60 min of reperfusion, LVEDP had recovered in all groups to similar values.

Recovery of contractile function during reperfusion

Figure 1 (top) shows recovery of LVDP as an index of contractile function. During baseline conditions, LVDP was similar in all groups. During reperfusion after ischaemia, recovery of LVDP was very poor in the control group, reaching only 13 (2)% of baseline values at 60 min of reperfusion. Administration of all inhalation anaesthetics resulted in improved functional recovery that was similar for all agents at 60 min of reperfusion (33 (3)% of baseline; $P<0.05$). However, the time course of recovery was different for the agents: halothane, enflurane and isoflurane showed a similar pattern of recovery (fig. 1, top left), starting with a gradual recovery of LVDP during the initial 30 min of reperfusion when the inhalation anaesthetics were present, followed by a further increase in LVDP by 18% after anaesthetic withdrawal. Sevoflurane showed a similar pattern of recovery during the first 30 min of reperfusion, but there was no further functional improvement after its withdrawal (fig. 1, top right). Desflurane showed a different pattern, reaching the final state of functional recovery within the first 2 min of reperfusion. Recovery of dP/dtmax as an index of myocardial contractility was parallelled by recovery of LVDP (table 2).

Table 2 Haemodynamic variables during the ischaemia–reperfusion experiments. Data are mean (SEM), $n=6$. CPP=Coronary perfusion pressure; LVEDP=left ventricular end-diastolic developed pressure; d*P*/d*t*max=maximum velocity of the change in left ventricular pressure; $\dot{V}o_2$=myocardial oxygen consumption. *$P<0.05$ compared with controls;†$P<0.05$ compared with baseline

		Reperfusion			
		Inhalation anaesthetic			
	Baseline	5 min	25 min	30 min	60 min
CPP (mm Hg)					
Control	87.1 (10.5)	105.8 (4.6)	109.2 (7.6)	111.7 (7.8)	121.6 (9.4)
Halothane	75.2 (8.3)	93.9 (7.0)	97.2 (7.4)	101.8 (8.0)	118.8 (7.5)†
Isoflurane	72.4 (10 3)	101.9 (5.1)†	103.8 (5.7)†	101.7 (5.3)†	114.5 (6.7)†
Enflurane	75.7 (9.7)	97.0 (6.0)	99.1 (7.9)	97.3 (8.0)	114.6 (10.3)†
Sevoflurane	74.4 (9.2)	106.2 (4.0)	125.3 (15.6)†	142.1 (14.7)†	150.9 (16.4)†
Desflurane	81.0 (17.3)	83.0 (3.5)*	98.7 (8.6)	105.7 (10.0)	129 5 (13.7)†
LVEDP (mm Hg)					
Control	4.9 (0.5)	133.4 (5.7)†	89.4 (4.1)†	85.6 (4.1)†	78.8 (4.5)†
Halothane	4.9 (0.5)	116.7 (7.7)†	81.4 (7.1)†	76.6 (8.9)†	83.9 (7.6)†
Isoflurane	5.5 (0.7)	115.5 (10.1)†	72 0 (6.4)†	67.2 (6.2)†	72.3 (3.3)†
Enflurane	4.5 (0.4)	104.7 (7.8)†	67.0 (5.6)*†	59.1 (6.4)*†	68.8 (8.0)†
Sevoflurane	4.0 (0.7)	106.2 (8.5)†	68.4 (4.9)†	70.0 (2.6)†	60.7 (4.1)†
Desflurane	5.5 (0.5)	101.6 (4.4)*†	71.4 (3.1)†	74.3 (4.1)†	77.7 (8.2)†
d*P*/d*t*max (mm Hg s^{-1})					
Control	3617 (296)	680 (90)†	839 (68)†	956 (96)†	1012 (101)†
Halothane	3237 (356)	804 (147)†	1300 (172)†	1717 (381)†	1339 (232)†
Isoflurane	3115 (183)	667 (111)†	1218 (243)†	1474 (244)†	1210 (134)†
Enflurane	3054 (174)	670 (60)†	1265 (157)†	1730 (300)†	1378 (248)†
Sevoflurane	3181 (250)	661 (62)†	1284 (147)†	1386 (184)†	1340 (135)†
Desflurane	3092 (188)	1288 (75)*†	1754 (127)*†	1733 (64)†	1457 (110)†
$\dot{V}o_2$ (µl min^{-1})					
Control	184.8 (9.5)	178.6 (8.6)	118.8 (14.1)†	112.1 (14.6)†	104.8 (17.3)†
Halothane	170.7 (13.1)	161.9 (15.5)	129.0 (6.5)	157.7 (5.9)	133.6 (9.1)
Isoflurane	161.5 (6.8)	164.8 (11.4)	111.9 (8.7)†	130.0 (6.8)	117.6 (6.4)†
Enflurane	158.5 (11.9)	173.7 (5.6)	149.0 (16.8)	161.8 (9.2)	137.0 (7.7)
Sevoflurane	149.5 (7.3)	200.7 (13.2)	168.5 (17.5)	159.3 (14.9)*	146.2 (14.6)
Desflurane	163.6 (9.3)	171.0 (6.9)	146.9 (11.7)	139.4 (13.7)	119.3 (18.7)

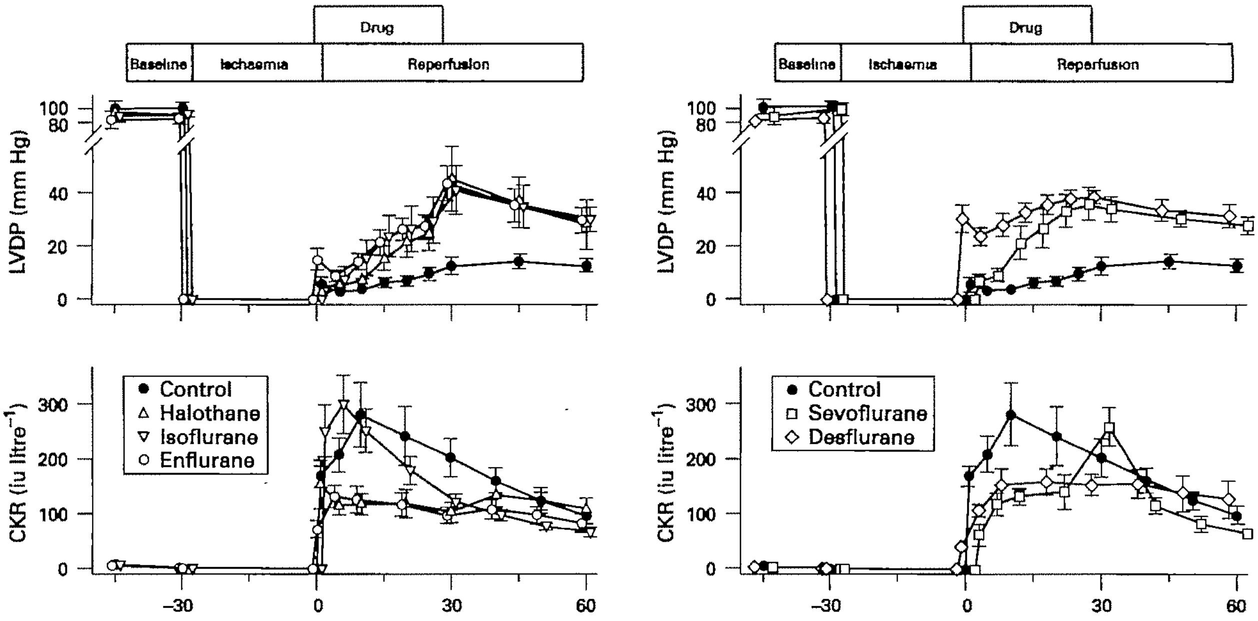

Figure 1 Time course of left ventricular developed pressure (LVDP) as an index of myocardial function and creatine kinase release (CKR) as an index of cellular injury. Controls are the same on the left and right side of the figure. Drug=time when 1.5 MAC of the respective inhalation anaesthetic was added to the perfusion medium.

Coronary vascular resistance during reperfusion

CPP is a direct measure of coronary vascular resistance in this experimental model because coronary flow was kept constant (table 2). With the onset of reperfusion, CPP increased to 130% of baseline in the control group. This initial increase in CPP after ischaemia was similar in the presence of halothane (to 125%), enflurane (to 128%), isoflurane (to 140%) and sevoflurane (to 143%) and was absent in the presence of desflurane (to 102%, $P<0.05$ *vs* control). In all groups, there was a further progressive increase in CPP during the reperfusion period which was most pronounced in the sevoflurane group.

METABOLIC MEASUREMENTS

Creatine kinase

CK activity in the coronary venous effluent was determined as an index of cellular injury (fig. 1, bottom). In the control group, CKR increased rapidly during the early reperfusion period with a peak value of 283 iu litre^{-1} at 10 min of reperfusion. This initial peak CKR was markedly attenuated by halothane, enflurane, sevoflurane and desflurane (to 42%, 45%, 47% and 39% of the peak CKR in the untreated controls). Isoflurane had no effect on initial cellular injury and peak CKR was similar to that of controls (107% of controls). Although sevoflurane markedly attenuated the early peak CKR, a delayed peak CKR occurred immediately after removal.

Oxygen consumption

During baseline conditions, $\dot{V}O_2$ was not different between groups. With the onset of reperfusion, $\dot{V}O_2$ of the reperfused myocardium was as high as during baseline conditions in all groups, despite the markedly reduced contractile state. In the control group, $\dot{V}O_2$ then rapidly declined during reperfusion to 56% of baseline at the end of the reperfusion period ($P<0.05$). In the groups treated with inhalation anaesthetics, $\dot{V}O_2$ during reperfusion tended to be higher than in untreated controls, but also declined during reperfusion in the halothane (to 78%), isoflurane (to 72%) and enflurane groups (to 86% of baseline at 60 min of reperfusion). $\dot{V}O_2$ remained at the pre-ischaemic baseline level in the sevoflurane group (97% of baseline at 60 min of reperfusion) (table 2).

Discussion

The main finding of our study was that all inhalation anaesthetics offered some protective effect against reperfusion injury in the heart. However, there were differences in the effects on cellular injury (which was attenuated by all anaesthetics except isoflurane) and functional recovery (which was improved by all agents to a similar degree, but with a different time course). These differences suggest different protective mechanisms, which have to date been characterized at a cellular level for only halothane.

critique of methods

Five hearts received four different inhalation anaesthetics each for assessment of the haemodynamic effects on normal myocardium in this experimental preparation. Although these interventions were made in a randomized order, effects of previous exposure to a different anaesthetic cannot be excluded. However, the data confirm a myocardial depressant effect of all anaesthetics in this preparation.

Our study used an isolated buffer perfused heart model, which has the advantage of excluding most haemodynamic and humoral side effects of inhalation anaesthetics. But a myocardial depressant effect of the anaesthetics was observed in the present model and was shown by a reduction in LVDP and d*P*/d*t*max in non-ischaemic hearts. However, during reperfusion, LVDP was higher in most of the treatment groups compared with controls, which makes it unlikely that changes in ventricular pressure were responsible for the protective effect. While the experimental model of our study was designed to assess direct myocardial effects of inhalation anaesthetics on reperfusion injury, at the same time it excluded several mechanisms that may also be important in the *in vivo* situation of ischaemia and reperfusion, such as changes in global haemodynamics and sympathetic nervous system activity, and activation of neutrophils in reperfused myocardium (for review see Mullane and Young[8]). Consequently, the effect of the inhalation anaesthetics *in vivo* may be different from what was observed in our study. For halothane, isoflurane and sevoflurane it has been shown that they can reduce post-ischaemic accumulation of neutrophils in reperfused myocardium,[9] which may be an important protective mechanism *in vivo*.

As the danger of impeding hypercontracture in the reoxygenated myocardium is evoked by reactivation of mitochondrial energy production,[10] a protective agent should be present in the myocardium at the onset of reoxygenation. Therefore, we started the supply of the inhalation anaesthetics with a 2-min anoxic wash-in before reperfusion with the oxygenated buffer. During anoxic perfusion there was no change in LVEDP as an index of myocardial contracture, while LVEDP increased immediately with the onset of reperfusion with oxygenated buffer. In a previous study we have shown that during anoxic perfusion, there is no significant CK release, indicating the absence of lethal cellular injury at this time.[1] Thus it is unlikely that this short period of anoxic perfusion itself had an effect on ischaemia–reperfusion injury in this study. In addition, the control hearts also underwent a similar anoxic perfusion programme as the treatment hearts.

INTERPRETATION OF RESULTS

Reperfusion of myocardium after a prolonged period of ischaemia initiates cellular and biochemical changes which reduce the amount of potentially salvageable myocardium and impair the contractile function of the surviving myocardium ("reperfusion injury"). The term "lethal reperfusion injury" was introduced for the irreversible deterioration of myocardium that can be avoided by modifications of the conditions of reperfusion.[11] If the preceding ischaemia is less severe, reperfusion results in a reversible state of non-lethally injured myocardium showing contractile dysfunction: "myocardial stunning".[12]

For halothane, a specific protective effect against reperfusion injury had been demonstrated that can be separated from its anti-ischaemic effects.[1] Several studies have described protective effects of enflurane and isoflurane in ischaemia–reperfusion situations: enflurane and isoflurane improved post-ischaemic functional recovery of isolated hearts after cardioplegic arrest,[13] after hypoxic perfusion (isoflurane)[14], after global ischaemia (enflurane,[15] isoflurane)[16] and after 1-day hypothermic preservation (isoflurane).[17] *In vivo*, attenuation of myocardial stunning was found for isoflurane in dogs.[18–20] However, from these studies, it was not possible to distinguish anti-ischaemic effects from effects on myocardial reperfusion injury because in these studies the inhalation anaesthetics were given before the onset of ischaemia or during the ischaemic period. In the *in vivo* studies, the haemodynamic effects of the inhalation anaesthetics (i.e. a reduction in sympathetic tone, myocardial inotropy and myocardial work) may also have contributed to the observed protective effects. For sevoflurane and desflurane, only anti-ischaemic effects have been studied to date,[21 22] but there are no studies investigating the effects of these agents during reperfusion. Therefore, in this study we used isolated hearts where systemic haemodynamic effects are absent and where the substances were given selectively during the initial reperfusion period only.

In a previous study we used a similar isolated heart model for demonstration of a pronounced protective effect against reperfusion injury by halothane.[1] In that study, "ischaemia" was simulated by anoxic perfusion in order to administer halothane during "ischaemia" also. However, anoxic perfusion partially eliminates the metabolic waste from the ischaemic myocardium and may thereby modify ischaemia–reperfusion injury. In this study, we used no-flow ischaemia followed by reperfusion, which comes closer to the *in vivo* situation of ischaemia–reperfusion. Our previous study showed that halothane reduced lethal cell damage during reperfusion and led to improved functional recovery. These findings were confirmed in our study. We expected that the other volatile anaesthetics would protect against reperfusion injury in a similar manner. Surprisingly, they had different effects when given during reperfusion: only enflurane was comparable with halothane; during desflurane administration, functional recovery occurred more rapidly; isoflurane had no effect on lethal cell damage but improved functional recovery; and with sevoflurane, lethal cell damage was delayed and occurred after discontinuation of the anaesthetic. However, functional recovery with sevoflurane was similar to that seen in the presence of halothane, enflurane or isoflurane.

Recovery of contractile function

In experimental models such as ours, functional recovery depends mainly on two factors.[23] First, the amount of lethally injured myocardium can limit the extent of functional recovery by a reduction in contractile mass. Second, even after short periods of ischaemia, contractile function of non-lethally injured myocardium is depressed and may need several hours or days for full recovery. This phenomenon is termed "myocardial stunning". Consequently, the effect of inhalation anaesthetics on recovery of myocardial function may be explained by one or both of these mechanisms. In the desflurane group, a transient positive inotropic effect may have contributed to the time course of functional recovery: only during desflurane administration was there rapid improvement in contractility within the first minutes of reperfusion to close to the final state of functional recovery. Desflurane also showed a small initial positive inotropic effect in the normoxic control hearts, which is most likely caused by direct catecholamine release from autonomic nerve endings.[24] It is well known that stunned myocardium responds well to inotropic stimulation,[25] and this initial positive inotropic effect of desflurane may be responsible for the initial rapid improvement in contractile function in this group.

Lethal cellular injury

With the onset of reperfusion, $\dot{V}o_2$ was high in the control hearts and then declined rapidly during the initial reperfusion period, while simultaneously, CK was released from the myocardium indicating the occurence of lethal reperfusion injury during this time. Isoflurane was the only inhalation anaesthetic that had no effect on CKR during reperfusion or on $\dot{V}o_2$ compared with controls. Sevoflurane delayed CKR until its discontinuation. The lack of a protective effect of isoflurane against lethal cell damage was also observed in isolated working rat hearts (where halothane or isoflurane were given also before ischaemia and during reperfusion) and *in vivo* in rabbits, where isoflurane failed to reduce myocardial infarct size after coronary occlusion and reperfusion.[26 27] The finding of improved functional recovery of post-ischaemic myocardium in the presence of isoflurane is in accordance with two previous *in vivo* studies that also found attenuation of myocardial stunning in non-lethally injured myocardium.[18 19] The mechanisms leading to cell death and myocardial stunning may differ slightly (for review see Hearse and Bolli[23]). Therefore, the difference in protective effects against lethal cell damage and myocardial stunning also suggests different protective effects of inhalation anaesthetics given during reperfusion against these two forms of myocardial reperfusion injury.

The concept of early lethal reperfusion injury was developed from investigation of isolated anoxic–reoxygenated heart cells.[28] Here it was shown that the critical phase for development of early lethal reperfusion injury is the first minutes after resupply of oxygen, when intracellular calcium overload[29] and SR dysfunction[6] may trigger cellular hypercontracture and cell death. From these findings, it was concluded that a protective agent could be discontinued after this critical time.[28] This concept of early discontinuation of the protective substances worked in our experimental model for halothane, enflurane and desflurane, but not for sevoflurane, which showed a delayed peak CKR after discontinuation, indicating the occurrence of lethal cellular injury at this time. However, the total amount of CK released from the reperfused myocardium was also reduced by sevoflurane. The reason for these differences is unknown but suggests a different action of sevoflurane on post-ischaemic myocardium. For halothane, the protective mechanism against lethal reperfusion damage of the "oxygen paradox" type was recently identified[3 4]: halothane prevented the rapid Ca^{2+} cycling of the sarcoplasmic reticulum (SR) that is found during reoxygenation after a severe ischaemic insult. These Ca^{2+} oscillations occur at the calcium release channel (ryanodine receptor) of the SR and are responsible for cellular hypercontracture and cell death during early reperfusion.[6] Data from non-ischaemic–reperfused isolated heart cells showed that halothane and enflurane but not isoflurane act on this calcium release channel of the SR.[30]

The finding that isoflurane does not influence SR calcium release channel may explain the failure of isoflurane to protect against early lethal reperfusion injury. The action of sevoflurane on this channel is still unknown. However, except for halothane, the mechanisms of myocardial protection against lethal reperfusion injury by inhalation anaesthetics have not been investigated. They do not seem to be related to the negative inotropic effects of the agents; both halothane, which has the most pronounced negative inotropic effects in isolated hearts during normoxia (this study) or during post-ischaemic periods,[21] and desflurane, which has the lowest negative inotropic effects, were comparable with regard to myocardial protection. This example also argues against a simple relationship between the protective effect and physicochemical properties (such as lipid solubility, which is lowest for desflurane and highest for halothane but both offered similar protection, and intermediate for isoflurane which had no protective effect against lethal cell injury).

In summary, the results of our study provide some evidence that inhalation anaesthetics have different mechanisms of protection against reperfusion injury, but further experimental work is needed to clarify these mechanisms at the cellular level.

Acknowledgement

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References

1. Schlack W, Hollmann M, Stunneck J, Thamer V. Effect of halothane on myocardial reoxygenation injury in the isolated rat heart. *British Journal of Anaesthesia* 1996; **76**: 860–867.
2. Schlack W, Preckel B, Barthel H, Obal D, Thamer V. Halothane reduces reperfusion injury after regional ischaemia in the rabbit heart in vivo. *British Journal of Anaesthesia* 1997; **79**: 88–96.
3. Schlack W, Siegmund B, Piper HM. Protective mechanism of halothane on myocardial reperfusion injury. *British Journal of Anaesthesia* 1996; **76** (Suppl. 2): 41.
4. Schlack W, Siegmund B, Piper HM. Protection of isolated cardiomyocytes against reoxygenation-induced hypercontracture by halothane. In: Grothe J. ed. *Funktionsanalyse biologischer Systeme*. Stuttgart: Gustav Fischer, 1998; in press.
5. Siegmund B, Schlack W, Ladilov YV, Piper HM. Halothane protects cardiomyocytes against reoxygenation-induced hypercontracture. *Circulation* 1997; **96**: 4372–4379.
6. Ladilov YV, Siegmund B, Piper HM. Protection of reoxygenated cardiomyocytes against hypercontracture by inhibition of Na+/H+ exchange. *American Journal of Physiology* 1995; **268**: H1531–H1539.
7. Abel FL. Maximal negative dP/dt as an indicator of end of systole. *American Journal of Physiology* 1981; **240**: H676–H679.
8. Mullane KM, Young M. The contribution of neutrophil activation and changes in endothelial function to myocardial ischemia–reperfusion injury. In: Yellon DM, Jennings RB, eds. *The Pathophysiology of Reperfusion and Reperfusion Injury*. New York: Raven Press, 1992; 59–83.
9. Kowalski C, Zahler S, Becker BF, Flaucher A, Conzen PF, Gerlach E, Peter K. Halothane, isoflurane, and sevoflurane reduce postischemic adhesion of neutrophils in the coronary system. *Anesthesiology* 1997; **86**: 188–195.
10. Piper HM. Mitochondrial injury in the oxygen-depleted and reoxygenated myocardial cell. In: Piper HM, ed *Pathophysiology of Severe Ischemic Injury*. Dordrecht: Kluwer Academic, 1990; 91–114.
11. Rosenkranz ER, Buckberg GD. Myocardial protection during surgical coronary reperfusion. *Journal of the American College of Cardiology* 1983; **1**: 1235–1246.
12. Bolli R. Mechanism of myocardial "stunning". *Circulation* 1990; **82**: 723–737
13. Coetzee A, Skein W, Genade S, Lochner A. Enflurane and isoflurane reduce reperfusion dysfunction in the isolated rat heart. *Anesthesia and Analgesia* 1993; **76**: 602–608
14. Marijic J, Stowe DF, Turner LA, Kampine JP, Bosnjak ZJ. Differential protective effects of halothane and isoflurane against hypoxic and reoxygenation injury in the isolated guinea pig heart. *Anesthesiology* 1990; **73**: 976–983.
15. Freedman BM, Hamm DP, Everson CT, Wechsler AS, Christian TF. Enflurane enhances postischemic functional recovery in the isolated rat heart. *Anesthesiology* 1985, **62**. 29–33.
16. Mattheussen M, Rusy BF, Van Aken H, Flameng W Recovery of function and adenosine triphosphate metabolism following myocardial ischemia induced in the presence of volatile anesthetics. *Anesthesia and Analgesia* 1993; **76**: 69–75.
17. Stowe DF, Heisner J, Bosnjak ZJ, Fujita S. Isoflurane improves contractility and coronary flow in isolated hearts after one day hypothermic preservation. A KATP channel role? *Anesthesiology* 1996; **85** (Suppl. 3a): A551.
18. Warltier DC, Al-Wathiqui MH, Kampine JP, Schmeling WT. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* 1988; **69**: 552–565.
19. Kanaya N, Fujita S. The effects of isoflurane on regional myocardial contractility and metabolism in "stunned" myocardium in acutely instrumented dogs. *Anesthesia and Analgesia* 1994; **79**: 447–454.
20. Kersten JR, Schmeling TJ, Hettrick DA, Pagel PS, Gross GJ, Warltier DC. Mechanism of myocardial protection by isoflurane. Role of adenosine triphosphate-regulated potassium (KATP) channels. *Anesthesiology* 1996; **85**: 794–807
21. Oguchi T, Kashimoto S, Yamaguchi T, Nakamura T, Kumazawa T. Comparative effects of halothane, enflurane, isoflurane and sevoflurane on function and metabolism in the ischaemic rat heart. *British Journal of Anaesthesia* 1995, **74**: 569–575.
22. Pagel PS, Hettrick DA, Lowe D, Tessmer JP, Warltier DC Desflurane and isoflurane exert modest beneficial actions on left ventricular diastolic function during myocardial ischemia in dogs. *Anesthesiology* 1995; **83**: 1021–1035.
23. Hearse DJ, Bolli R. Reperfusion induced injury: manifestations, mechanisms and clinical relevance. *Trends in Cardiovascular Medicine* 1991; **1**: 233–240.
24. Gueugniaud PY, Hanouz JL, Vivien B, Lecarpentier Y, Coriat P, Riou B Effects of desflurane in rat myocardium. Comparison with isoflurane and halothane. *Anesthesiology* 1997; **87**: 599–609.
25. Ito BR, Tate H, Kobayashi M, Schaper W. Reversibly injured, postischemic canine myocardium retains normal contractile reserve. *Circulation Research* 1987; **61**: 834–846.
26. Preckel B, Schlack W, Obal D, Thamer V. Different effects of enflurane, isoflurane, sevoflurane, and desflurane on myocardial reperfusion injury in vivo. *British Journal of Anaesthesia* 1997; **78** (Suppl. 1): 45.
27. Preckel B, Schlack W, Comfere T, Barthel H, Obal D, Thamer V. Effects of enflurane, isoflurane, sevoflurane and desflurane on reperfusion injury after regional myocardial ischaemia in the rabbit heart *in vivo*. *British Journal of Anaesthesia* 1998; **81**: 905–912.
28. Siegmund B. Schluter KD, Piper HM. Calcium and the oxygen paradox. *Cardiovascular Research* 1993; **27**: 1778–1783.
29. Siegmund B. ZudeR. Piper HM. Recovery of anoxic–reoxygenated cardiomyocytes from severe Ca^{2+} overload *American Journal of Physiology* 1992; **263**: H1262–H1269.
30. Wheeler DM, Rice RT, DuBell WH, Spurgeon HA. Initial contractile response of isolated rat heart cells to halothane, enflurane, and isoflurane. *Anesthesiology* 1997; **86**: 137–146.

British Journal of Anaesthesia 1998; **81**: 920–924

Milrinone decreases both pulmonary arterial and venous resistances in the hypoxic dog

R. KATO, J. SATO AND T. NISHINO

Summary

We have studied the effect of milrinone on pulmonary vascular resistance (PVR) in dogs with hypoxic pulmonary vasoconstriction (HPV). Using a pulmonary arterial occlusion method, we measured effective pulmonary capillary pressure (Pcap) by which total PVR was partitioned into arterial (PVRa) and venous (PVRv) components. Hypoxic ventilation ($F_{I_{O_2}}$=0.11–0.13) produced significant increases in mean pulmonary arterial pressure (PAP) and Pcap (P<0.01) associated with increases in PVRa and PVRv (P<0.01). During the hypoxic period, milrinone significantly decreased mean PAP and Pcap (P<0.01), reflected in decreases in PVRa and PVRv (P<0.01). The longitudinal distribution of PVR (PVRa/PVRv) remained unchanged throughout the experiment, indicating that HPV occurred equally in the arterial and venous segments and that milrinone-induced vasodilatation occurred equally in both segments. During hypoxia, milrinone did not produce an increase in cardiac output or a decrease in Pa_{O_2}. Milrinone also produced significant decreases in mean systemic arterial pressure (P<0.01) and systemic vascular resistance (P<0.05) to a similar extent to the decreases in mean PAP and PVR, suggesting no selective dilating effect of milrinone on the pulmonary vasculature. These results indicate that in HPV, milrinone decreased the vascular tone of both pulmonary arterial and venous segments without increasing cardiac work or impairing pulmonary oxygenation. This suggests a potential for use in patients suffering from hypoxic pulmonary hypertension. (*Br. J. Anaesth.* 1998; **81**: 920–924).

Keywords: pharmacology, milrinone; cardiorespiratory system, effects; lung, intravascular pressures; hypoxia; lung, vasculature; dog

Hypoxic pulmonary vasoconstriction (HPV) plays an important role in inducing pulmonary hypertension in several acute and chronic lung diseases, including the acute respiratory distress syndrome (ARDS), pulmonary oedema, pulmonary embolism, chronic obstructive airways disease and pulmonary fibrosis.[1] Although HPV is a physiological adaptation to alveolar hypoxia,[2] associated pulmonary hypertension may produce adverse effects, particularly in patients suffering from cardiovascular dysfunction.[3 4] Milrinone, a phosphodiesterase III inhibitor, is used to improve pulmonary haemodynamics in association with systemic haemodynamic dysfunction.[3–5] Several workers have advocated the preferential effect of milrinone on pulmonary haemodynamics over systemic haemodynamics in pulmonary hypertension.[3 4 6] However, to our knowledge no study has focused on the effect of milrinone on pulmonary hypertension produced by HPV or the effector site of milrinone in the pulmonary vascular tree.

Therefore, the aims of this study were to examine if milrinone improves pulmonary haemodynamics in acute HPV and, if it does, to explore if milrinone produces differential vasodilating effects in the pulmonary vascular tree. To assess the longitudinal distribution of pulmonary vascular resistance (PVR), we used a pulmonary arterial occlusion technique.[7–9] This technique estimates effective pulmonary capillary pressure (Pcap) by which PVR is partitioned into arterial and venous components.

Materials and methods

This study was approved by the Animal Welfare Committee, Laboratory Animal Centre, School of Medicine, Chiba University.

ANIMAL PREPARATION

We studied seven healthy mongrel dogs (aged 3–5 yr, weight 12–20 (mean 16.7) kg) premedicated with ketamine 10 mg kg^{-1} i.m. Anaesthesia was induced by pentobarbital, 20–40 mg kg^{-1} i.v. and maintained by continuous infusion of pentobarbital (pentobarbitone) 5–10 mg kg^{-1} h^{-1}. The dogs were paralysed with pancuronium 0.1 mg kg^{-1} at hourly intervals, the trachea intubated and the lungs ventilated mechanically with 30–40% oxygen in nitrogen. Respired gas was sampled continuously at the proximal end of the tracheal tube to monitor inspired oxygen and end-tidal carbon dioxide tensions (Anaesthetic Gas Monitor Type 1304, Bruel & Kjaer, Copenhagen, Denmark). Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide partial pressure at 4.0–5.3 kPa. Lactate Ringer's solution 6 ml kg^{-1} h^{-1} i.v. was administered for maintenance fluid replacement. The surface ECG (lead II) was monitored with skin needle electrodes. Rectal temperature was maintained at approximately 37°C using an overhead heating lamp.

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HAEMODYNAMIC MEASUREMENTS

We measured systemic arterial pressure (SAP) continuously via a catheter inserted into the right femoral artery (L989–39, Abbot Critical Care Systems, Tokyo, Japan and 78534A Hewlett Packard, Silicon Valley, CA, USA). Pulmonary arterial pressure (PAP) was measured via a 5-French gauge pulmonary artery catheter (Arrow, Reading, PA, USA) inserted into the pulmonary artery via the right femoral vein. Central venous pressure (CVP) was measured via the side port of the pulmonary artery catheter at 3-min intervals. Continuous measurement of cardiac output (CO) was performed using an 8-French gauge catheter inserted into the pulmonary artery from the left femoral vein and connected to a thermodilution CO monitor (Intelicath and Vigilance, Baxter Healthcare, Irvine, CA, USA).

All haemodynamic data were stored on personal computer for offline analysis.

EXPERIMENTAL SEQUENCE

We started haemodynamic measurements after obtaining stable circulatory conditions after recovery from the surgical procedure and instrumentation. Our experimental sequence consisted of four phases of 30 min duration each: (1) control, (2) hypoxia (HYPO), (3) hypoxia+milrinone (H-M) and (4) milrinone (MIL). After control measurements at 3-min intervals during mechanical ventilation with 30–40% oxygen in nitrogen, hypoxia was induced by suddenly changing the inspired gas composition to 11–13% oxygen in nitrogen and measurements were repeated at 3-min intervals (HYPO). After a 30-min HYPO phase, a loading dose of milrinone 60 mg kg^{-1} followed by continuous infusion of 6 mg kg^{-1} h^{-1} was started and all the measurements were repeated (H-M). This milrinone regimen has been reported to produce therapeutic plasma concentrations for treatment of left ventricular dysfunction in humans.[10] Finally, $F\text{I}_{O_2}$ was restored to control values and measurements were performed every 3 min (MIL).

Each measurement included determination of CO and CVP values, together with 25-s data sampling of SAP and PAP.

PULMONARY ARTERIAL OCCLUSION TECHNIQUE AND CALCULATION OF PULMONARY AND SYSTEMIC HAEMODYNAMICS

We used a pulmonary artery occlusion technique for the intact lung preparation developed by Hakim and colleagues to estimate Pcap.[7 8] At end-expiration, mechanical ventilation was stopped and 25-s data sampling started. Ten seconds after the start of data sampling, pulmonary arterial occlusion for 15 s was performed by inflating the pulmonary artery catheter balloon instantaneously. This technique estimates Pcap from the pressure decay curve after pulmonary artery occlusion. The theory of the occlusion method is presented in figure 1. Pcap was noted as the pressure at the point where the monoexponential fitting curve merged with the measured pressure decay curve. More commonly used is the method which estimates Pcap by extrapolating the fitting curve to the instant of occlusion. However, we adopted the merging method as the instant of occlusion could not be identified precisely because of relatively slow inflation of the catheter balloon compared with rapidly responding occluders such as solenoid valves.

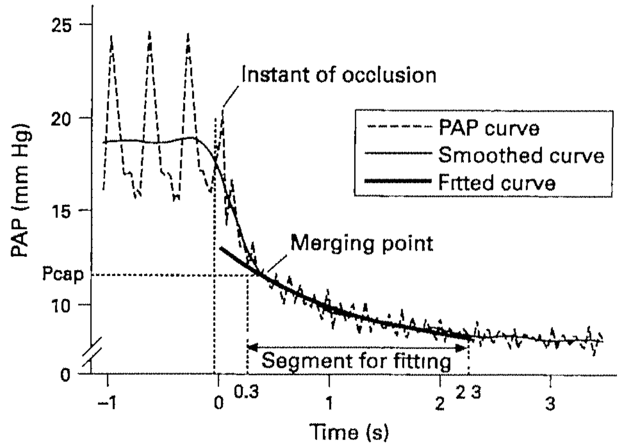

Figure 1 Theory of the occlusion method. The instant of occlusion was assumed to be the moment when the pressure waveform, on visual inspection, deviated from the expected pattern for pulmonary arterial pressure. The pulmonary artery pressure (PAP) signal was smoothed by low-pass filtering at the corner frequency of 1.5 Hz. The 2-s segment of the filtered signal starting at 0.3 s after occlusion was fitted with a single exponential curve. Pcap was estimated as the pressure at the instant when the filtered signal merged with the fitted curve. The smoothing was performed as the raw pressure signal during occlusion exhibited small oscillations which made it difficult to identify the merging point

It has been reported that in various pulmonary haemodynamic conditions, although the merging point method underestimated Pcap slightly, the difference between the estimated and "true" Pcap was within the range of experimental and computational errors and the estimated Pcap was able to track the changes in "true" Pcap.[8 9] Pulmonary microvascular pressure is known to be pulsatile,[7 8] indicating that the estimated Pcap varies according to the point in the cardiac cycle at which the pulmonary artery is occluded. Therefore, the mean of the two measurements obtained from occlusions at the systolic and diastolic phases was termed Pcap. Pulmonary arterial wedge pressure (PAWP) was obtained as the mean pressure at 10–11 s after occlusion.

Mean SAP (mSAP) and mean PAP (mPAP) were computed respectively from 8–10 heartbeats immediately before pulmonary arterial occlusion. Several studies showed that the CO measurement system used in this study exhibited a delayed time response when subjects exhibited unstable haemodynamics.[11] Therefore, we corrected CO for the delayed response time by applying a correction function obtained from published data.[11] Systemic vascular resistance (SVR) was defined as (mSAP–CVP)/CO.

Partitioning pulmonary vascular pressure gradient into pre- (arterial) and post-capillary (venous) components by Pcap, pulmonary arterial (PVRa) and venous (PVRv) resistances were defined as (mPAP–Pcap)/CO and (Pcap–PAWP)/CO, respectively. Thus total PVR (PVRtot)=PVRa+PVRv. Longitudinal distribution of PVR was defined as PVRv/PVRa.

BLOOD-GAS SAMPLING

Arterial and mixed venous blood-gas analyses were performed (Model 170 pH/Blood Gas Analyser, Ciba-Corning, Tokyo, Japan) every 20 min in each phase.

STATISTICAL ANALYSIS

Data were analysed by repeated measures analysis of variance followed by Student–Newman–Keuls test. $P<0.05$ was considered significant.

Results

Blood-gas data are shown in table 1. Both arterial pH and Pa_{CO_2} were within the physiological range throughout all phases. Pa_{O_2} decreased significantly during hypoxic ventilation but milrinone did not produce further changes in Pa_{O_2} (H-M *vs* HYPO). There was a similar trend in mixed venous oxygen tension ($P\bar{v}_{O_2}$) to that of Pa_{O_2}. Systemic haemodynamic data are shown in table 2. Hypoxia (HYPO) produced approximately 10% increases ($P<0.05$) in CO compared with control, and milrinone did not produce a further increase in CO (H-M and MIL). mSAP and SVR decreased significantly during administration of milrinone(H-M and MIL).

Figure 2 illustrates the changes in pulmonary haemodynamics. Both mPAP and Pcap increased significantly during HYPO compared with control ($P<0.01$) (fig. 2A). H-M produced significant decreases in mPAP, Pcap and PAWP compared with HYPO ($P<0.01$). HYPO produced significant increases in both PVRa and PVRv from control ($P<0.01$) (fig. 2B). Administration of milrinone (H-M) produced significant reductions in PVRtot, PVRa and PVRv which were increased during HYPO ($P<0.05$). After reversal of hypoxia (MIL), all pulmonary haemodynamic variables returned to control values. PVRv/PVRa remained unchanged throughout all phases (fig. 2C).

Figure 3 illustrates serial changes in PVR and its longitudinal distribution. Induction of hypoxia (HYPO) produced initial rapid increases in all three resistances (PVRtot, PVRa and PVRv), followed by further gradual increases. Milrinone produced a rapid reduction in the increased resistances, followed by a gradual reduction (H-M). PVRv/PVRa did not change throughout the four phases.

Table 1 Blood-gas data (mean (SEM), $n = 7$ dogs). $^{**}P<0\ 01$ compared with both control and HYPO; ††$P<0.01$ compared with both control and MIL.

	Control	HYPO	H-M	MIL
pH	7.39 (0.02)	7 41 (0.01)	7.38 (0.01)	7.36 (0.02)**
Pa_{CO_2} (kPa)	4.7 (0.3)	4.7 (0.3)	4.9 (0.3)	5.1 (0.3)
Pa_{O_2} (kPa)	17.9 (2.4)	6.0 (0.5)††	5.9 (0.4)††	20 0 (2.7)
$P\bar{v}_{O_2}$ (kPa)	6.7 (0.4)	4.7 (0.4)††	4.7 (0.4)††	7.3 (0.3)

Table 2 Systemic haemodynamic data (mean (SEM), $n = 7$ dogs). †$P<0.05$, ††$P<0.01$ compared with control; $^{*}P<0.05$, $^{**}P<0.01$ compared with HYPO

	Control	HYPO	H-M	MIL
CO (litre min^{-1})	2.4 (0.3)	2.7 (0.5)†	2.6 (0.3)†	2.4 (0.2)
mSAP (mm Hg)	121 (8)	131 (5)	105 (7)†**	95 (2)††**
SVR (mm Hg litre^{-1} min)	52 (8)	55 (7)	39 (3)†*	38 (3)†*

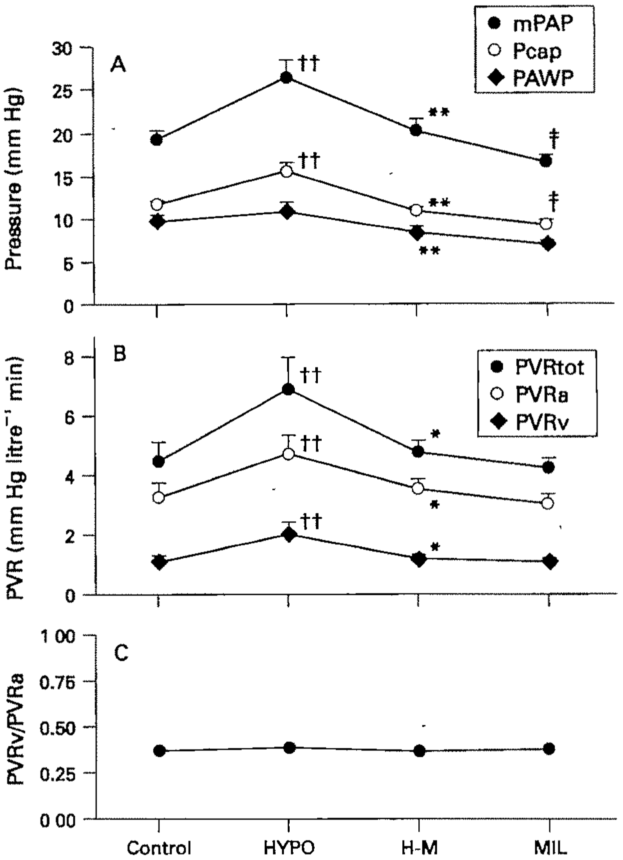

Figure 2 Changes in pulmonary haemodynamics (mean pulmonary artery pressure (mPAP), pulmonary capillary pressure (Pcap) and pulmonary artery wedge pressure (PAWP)) in the four phases: control, HYPO, H-M and MIL (A). Total pulmonary vascular resistance (PVRtot), pulmonary arterial resistance (PVRa) and pulmonary venous resistance (PVRv) in the four phases (B). Longitudinal distribution of PVR and PVRa/PVRtot in the four phases (C). All values are expressed as mean (SEM) (n=7 dogs). ††$P<0.01$ compared with control; $^{*}P<0.05$, $^{**}P<0.01$ compared with HYPO; ‡$P<0.05$ compared with H-M.

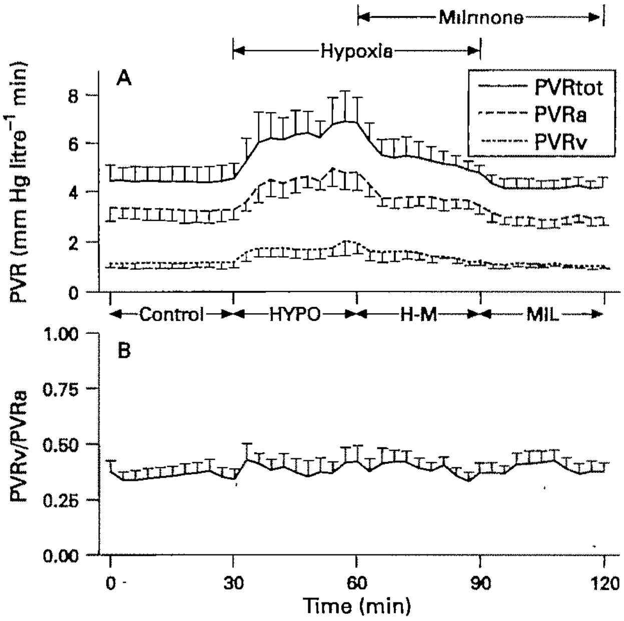

Figure 3 Serial changes in PVR (PVRtot, PVRa, and PVRv) and PVRv/PVRa. These were determined at 3-min intervals throughout the four phases. Values are mean (SEM) from seven dogs.

Discussion

Before discussing the implications of our results, we should consider what Pcap, estimated by our occlusion method, represents. Partitioning of PVR into arterial and venous segments by estimated Pcap depends on the theoretical model adopted for interpretation of the pulmonary arterial pressure decay curve after occlusion, and does not necessarily correlate precisely with anatomical structure. It is possible that the functional venous (post-capillary) segment defined by our method may include some anatomically arterial vessels in the pulmonary capillary segment, and vice versa. Thus it is important to note that the segments functionally partitioned by the occlusion method can only approximate to the mechanical characteristics of their anatomical correlates. With other reasons, such as experimental design and analytical methods, this functional and anatomical discordance could be an explanation for the wide range of longitudinal distribution of PVR reported in other studies, such as ~0.3–1.2 of PVRv/PVRa during hypoxia and normoxia.[12–16] Our results of 0.37 and 0.39 for PVRv/PVRa at control and HYPO, respectively, are at the lower end of the range of values reported by previous studies.

There are discrepancies as to the site of HPV, probably arising from differences in lung preparation, species, degree of hypoxia and measurement technique (occlusion device and adopted theoretical model). It has been reported that small arteries residing in the pre-capillary segment are the main site of vasoconstriction in response to alveolar hypoxia.[12–14] In contrast, recently published studies have indicated a significant contribution of the post-capillary venous segment in addition to the pre-capillary segment to the increase in PVR during alveolar hypoxia.[15,16] Hillier and colleagues demonstrated that alveolar hypoxia of a similar degree to that reported in this study produced active constriction of both arterioles and venules, even though these vessels lack obvious smooth muscle structure.[17] Contraction of the capillary arterioles and venules would result in increases in PVRa and PVRv, respectively, if our occlusion technique was used. Our finding that both PVRa and PVRv increased by the same magnitude is consistent with these studies.

The mechanism of the decrease in PVR produced by milrinone cannot be determined from our results. Passive pulmonary vasodilatation is induced by increased blood flow or increased distending pressure, or both.[18,19] In our case, however, this passive mechanism is unlikely as milrinone produced no significant change in CO and a 30% decrease in mPAP. Possible mechanisms might include direct relaxation of pulmonary vessels and recruitment of pulmonary vessels[20,21] associated with inter-regional redistribution of blood flow.

Some pulmonary vasodilators such as prostacyclin, prostaglandin E_1 and nitroglycerine are known to decrease PVRa and PVRv.[22–24] Alveolar hypoxia in the whole lung induces capillary recruitment and intrapulmonary blood flow redistribution towards well-ventilated lobes in an attempt to minimize the deterioration in pulmonary oxygenation.[2,21,25] Pulmonary vasodilatation produced by vasodilators hampers this adaptation process, resulting in increases in *Qs*/*Qt* and worsened pulmonary oxygenation.[20,23,24] In our study, milrinone did not worsen pulmonary oxygenation from the initial hypoxia. As milrinone did not change CO or $P\bar{v}_{O_2}$, it might not increase *Qs*/*Qt*. The reason why milrinone did not cause further deterioration in pulmonary oxygenation is not obvious from our results. However, the dose used in our study might have been relatively small and insufficient to increase cardiac output, which would have led to deleterious redistribution of pulmonary blood flow, but was still sufficient to produce pulmonary vasodilatation. This differential effect might be caused in part by the nitric oxide-like effect of milrinone.[26] Another possibility is that the decrease in capillary pressure reduced hyperaemia of the area where gas exchange was occurring, leading to improvement in gas exchange.[27] This would cancel out the ventilation–perfusion mismatching which would have been produced by milrinone-induced vasodilatation.

Reduction of PVR by milrinone may be beneficial in patients suffering from diseases characterized by increased Pcap with HPV, such as ARDS. These patients are susceptible to pulmonary oedema by pulmonary flow distribution imbalance[28] and the reduction of elevated Pcap by milrinone may therefore decrease the chance of pulmonary oedema.[9]

Absence of selective vasodilatation of the pulmonary vasculature by milrinone in our study may suggest that it has no potential use in the development of pulmonary hypertension induced by HPV However, our finding that milrinone reduced PVR with no increase in CO implies that milrinone may reduce right heart afterload without itself increasing cardiac work. Therefore, with a synergistic effect on systemic haemodynamics, milrinone might be of use in the treatment of pulmonary hypertension in patients with systemic cardiovascular disorders, in particular, right heart dysfunction.

References

1. Voelkel NF. Mechanisms of hypoxic pulmonary vasoconstriction. *American Review of Respiratory Disease* 1986; **133**: 1186–1195
2. Marshal BE, Marshal C, Frasch F, Hanson CW. Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. 2 Physiologic concepts *Intensive Care Medicine* 1994; **20**: 291–297
3. Harris MNE, Daborn AK, O'Dwyer JP Milrinone and the pulmonary vascular system. *European Journal of Anaesthesiology* 1992; (Suppl. 5): 27–30.
4. Feneck RO. Milrinone and postoperative pulmonary hypertension. *Journal of Cardiothoracic and Vascular Anesthesia* 1993; (Suppl. 1); 7: 21–23.
5. Chen EP, Bittner HB, Duane Davis R jr, Van Trigt P III Milrinone improves pulmonary haemodynamics and right ventricular function in chronic pulmonary hypertension. *Annals of Thoracic Surgery* 1997; **63**: 814–821.
6. Tanaka H, Tajimi K, Moritsune O, Kobayashi K, Okada K Effects of milrinone on pulmonary vasculature in normal dogs and in dogs with pulmonary hypertension. *Critical Care Medicine* 1991; **19**: 68–74.
7. Hakim TS, Marrek J-MI, Chang HK. Estimation of pulmonary capillary pressure in intact dog lungs using the arterial occlusion technique. *American Review of Respiratory Disease* 1989, **140**. 217–224.
8. Marrek J-MI, Hakim TS, Chang HK. Analysis of pulmonary arterial pressure profile after occlusion of pulsatile blood flow. *Journal of Applied Physiology* 1990, **68**: 761–769
9. Collee GG, Lynch KE, Hill RD, Zapol WM Bedside measurement of pulmonary capillary pressure in patients with acute respiratory failure. *Anesthesiology* 1987; **66**: 614–620

10. Makela VHM, Kapur PA. Is milrinone equivalent to amrinone during enflurane anesthesia in the dog? *Anesthesia and Analgesia* 1988; **67**: 349–355.
11. Siegel LC, Hennessy MM, Pearl RG. Delayed time response of the continuous cardiac output pulmonary artery catheter. *Anesthesia and Analgesia* 1996; **83**: 1173–1177.
12. Linehan JH, Dawson CA. A three-compartment model of the pulmonary vasculature: effects of vasoconstriction. *Journal of Applied Physiology* 1983; **55**: 923–928.
13. Siegel LC, Pearl RG, Shafer SL, Ream AK, Prielipp RC. The longitudinal distribution of pulmonary vascular resistance during unilateral hypoxia. *Anesthesiology* 1989; **70**: 527–532.
14. Audi SH, Dawson CA, Rickaby DA, Linehan JH. Localization of the sites of pulmonary vasomotion by use of arterial and venous occlusion. *Journal of Applied Physiology* 1991; **70**: 2126–2136.
15. Karen-Lise KW, Sanchez R, Ravn JB, Larsen B, Amtorp O. Effect of prolonged alveolar hypoxia on pulmonary arterial pressure and segmental vascular resistance. *Journal of Applied Physiology* 1993; **75**: 1194–1200.
16. Cremona G, Higenbottam T, Takao M, Bower E, Hall LW. Nature and site of action of endogenous nitric oxide in vasculature of isolated pig lungs *Journal of Applied Physiology* 1997; **82**: 23–31.
17. Hillier SC, Graham JA, Hanger CC, Godbey PS, Glenny RW, Wagner WW jr. Hypoxic vasoconstriction in pulmonary arterioles and venules. *Journal of Applied Physiology* 1997, **82**: 1084–1090.
18. Al-Tinawi A, Madden JA, Dawson CA, Linehan JH, Harder DR, Rickaby DA. Distensibility of small arteries of the dog lung. *Journal of Applied Physiology* 1991; **71**: 1714–1722.
19. Chammas JH, Rickeby DA, Guarin M, Linehan JH, Hanger CC, Dawson CA. Flow-induced vasodilation in the ferret lung. *Journal of Applied Physiology* 1997; **83**: 495–502.
20. Wagner WW jr, Latham LP, Capen RL. Capillary recruitment during airway hypoxia: role of pulmonary artery pressure. *Journal of Applied Physiology* 1979; **47**: 383–387.
21. Capen RL, Wagner WW jr. Intrapulmonary blood flow redistribution during hypoxia increases gas exchange surface area. *Journal of Applied Physiology* 1982; **52**: 1575–1581.
22. Pearl RG, Siegel LC. Effects of prostaglandin E_1 and hydralazine on the longitudinal distribution of pulmonary vascular resistance during vasoconstrictor pulmonary hypertension in sheep. *Anesthesiology* 1992; **76**: 106–112.
23. Radermacher P, Santak B, Becker H, Falke KJ. Prostaglandin E_1 and nitroglycerine reduce pulmonary capillary pressure but worsen ventilation–perfusion distribution in patients with adult respiratory distress syndrome. *Anesthesiology* 1989; **70**: 601–606.
24. Radermacher P, Santak B, Wust HJ, Tarnow J, Falke KJ. Prostacyclin for the treatment of pulmonary hypertension in the adult respiratory distress syndrome: effects on pulmonary capillary pressure and ventilation–perfusion distribution. *Anesthesiology* 1990; **72**: 238–244.
25. Neumann PH, Kivlen CM, Johnson A, Minnear FL, Malik AB. Effect of alveolar hypoxia on regional pulmonary perfusion. *Journal of Applied Physiology* 1984; **56**: 338–342.
26. Lindgren S, Anderddon KE. Effect of selective phosphodiesterase inhibitors on isolated coronary, lung and renal arteries from man and rat. *Acta Physiologica Scandinavica* 1991; **142**: 77–82.
27. Tranbaugh RF, Lewis FR. Mechanisms and etiologic factors of pulmonary edema. *Surgery, Gynecology and Obstetrics* 1984; **158**: 193–206.
28. Allen SJ, Drake RE, Katz J, Gabel JC, Laine GA. Lowered pulmonary arterial pressure prevents edema after endotoxin in sheep. *Journal of Applied Physiology* 1987; **63**: 1008–1011.

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Opioid receptor independent effects of morphine on membrane currents in single cardiac myocytes

C.-F. Hung, C.-H. Tsai and M-J. Su

Summary

We have examined the effects of morphine, a μ-opioid receptor agonist, on various membrane ionic currents in rat ventricular and human atrial myocytes, using patch-clamp techniques in the whole-cell configuration. Morphine produced a concentration-dependent reduction in peak transient sodium current. When the sodium current (I_{Na}) was evoked at 5-s intervals the estimated IC_{50} for morphine was approximately 30 μmol litre^{-1}. Morphine 10 μmol litre^{-1} inhibited I_{Na} with a 5-mV shift in the potential-dependent inactivation curve to negative potentials and retarded the I_{Na} recovery rate from the inactivated state. Use-dependent I_{Na} block was not observed when I_{Na} was elicited at frequencies varying from 0.2 to 20 Hz. Morphine did not significantly affect the inward calcium current (I_{Ca}), transient outward current (I_{to}) or the inwardly rectifying potassium current (I_{K1}) at a concentration of 30 μmol litre^{-1}. The inhibitory effect of morphine on I_{Na} could not be prevented or reversed by treatment with the opioid antagonist naloxone. Therefore, we suggest that morphine can directly inhibit the Na^+ inward current and bind to inactivated Na^+ channels. (*Br. J. Anaesth.* 1998; **81**: 925–931).

Key words: analgesics opioid, morphine; ions, sodium; ions, calcium; model, heart; receptors, opioid

Morphine, a μ-opioid receptor agonist, has been used clinically for the treatment of acute pulmonary oedema[1] and relief of myocardial infarct pain.[2] In addition, it has been shown to modify cardiac function. In isolated mammalian cardiac tissue,[3–5] morphine produces a negative inotropic and chronotropic effect. In addition, it has been reported to possess antiarrhythmic activity in guinea pig.[6] Electrophysiological studies in multicellular preparations showed that morphine decreased the maximum rate of action potential depolarization.[7 8] In contrast, the cardioprotective effect against ischaemia–reperfusion arrhythmia via activation of glibenclamide-sensitive potassium channels has also been found after repeated i.v. injections of morphine.[9 10] Despite numerous studies on the cardiac effects of morphine, the mechanism of action related to the cardiac inhibitory effect of this agent is still controversial and remains to be clarified. Moreover, there are at present no detailed accounts of the effect of morphine on membrane ionic currents in isolated cardiac myocytes.

Therefore, we designed these experiments to examine the ionic mechanisms responsible for the inhibitory action of morphine in single rat and human cardiac myocytes. The mode of action of morphine on the sodium channel was studied by direct measurement of the sodium current (I_{Na}) using a voltage-clamp technique.

Materials and methods

ISOLATION OF RAT VENTRICULAR MYOCYTES

Animal use in this study conformed with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication No. 85–23, revised 1985). Rat ventricular myocytes were isolated using a technique described previously.[11 12] Briefly, rats weighing 250–350 g were anaesthetized with pentobarbital sodium 50 mg kg^{-1} i.p. The hearts were excised and retrogradely perfused in a Langendorff apparatus with Ca^{2+}-free, HEPES-buffered Tyrode solution consisting of (mmol litre^{-1}): NaCl 137.0, KCl 5.4, $MgCl_2$ 1.1, dextrose 22.0, N-[2-hydroxyethyl] piperazine-N′-[2-ethanesulphonic acid] (HEPES) 10.0, with pH adjusted to 7.4 with NaOH. The perfusate was oxygenated and maintained at 37±0.2°C. After 5 min, the perfusate was changed to the same solution containing collagenase 0.5 mg ml^{-1} (Type I, Sigma Chemical Co., St Louis, MO, USA) and protease 0.1 mg ml^{-1} (Type XIV, Sigma). After 15–25 min of digestion, the residual enzymatic solution was cleaned with Ca^{2+}–HEPES-buffered Tyrode solution 0.05 mmol litre^{-1}. The ventricular tissue was then separated and small pieces of tissue were agitated gently. Isolated single cells were stored in Ca^{2+}–HEPES-buffered Tyrode solution 0.2 mmol litre^{-1} at room temperature (25–27°C) for later use. Cells were used within 10 h of isolation.

ISOLATION OF HUMAN ATRIAL MYOCYTES

The investigation of human preparations conformed to the principles outlined in the Declaration of Helsinki. Specimens of human right atrial appendages were obtained with consent from patients (25–60 yr)

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during the surgical procedure when starting extracorporeal circulation. Single atrial cells were isolated by a procedure modified slightly from those described previously.[13 14] Briefly, the tissue specimens were placed in chilled oxygenated Ca^{2+}-free, HEPES-buffered solution and were brought to the laboratory from the operating room. Samples of these tissue specimens were washed three times in the same solution and then gently stirred for 30 min in a similar solution containing collagenase 400 iu ml^{-1} (Type I, Sigma) and protease 4 iu ml^{-1} (Type XXVII, Sigma) at 35±0.2°C. Thereafter, the partially digested samples were transferred to a fresh enzymatic solution containing collagenase 400 iu ml^{-1}. Meanwhile, continuous microscopic examination of the enzymatic solution was performed to assess the number and quality of isolated cells. Finally, the isolated cells were washed and stored in Ca^{2+}–HEPES-buffered Tyrode solution 0.2 mmol litre^{-1} at room temperature for later use. Cells were used within 5 h of isolation.

ELECTROPHYSIOLOGICAL RECORDING

Transmembrane currents were measured using the tight-seal, whole-cell recording technique.[15] Single myocytes were placed in a recording chamber (1-ml volume) attached to an inverted microscope (Nikon, Diaphot, Japan) and perfused with Ca^{2+}–HEPES-buffered Tyrode solution 1.8 mmol litre^{-1}. The heat-polished glass pipettes were filled with internal solution and had tip resistances of 1–2 MΩ. A Dagan 8900 patch/whole-cell clamp amplifier fitted with 100 MΩ feedback resistor in the headstage was used to clamp the myocytes. Most experiments were performed at room temperature. The total series resistance for the pathway between the pipette interior and the cell membrane was estimated from the cell capacitance and capacitance current decay. The capacitive transient during a step change in potential was partially compensated with analogue circuitry. Series resistance was compensated by at least 60–80% and was usually less than 1 MΩ. The maximal expected voltage decrease across the uncompensated series resistance was less than 8 mV for the largest current recorded and therefore was not corrected.

During measurement of I_{Na} and I_{Ca}, the K$^+$ currents were blocked by addition of Cs$^+$ 1 mmol litre^{-1} to the bathing medium and internal dialysis of the cells with Cs$^+$ containing pipette solution consisting of (mmol litre^{-1}): CsCl 130.0, K$_2$EGTA 15.0, tetraethylammonium chloride (TEA Cl) 15.0, HEPES 10.0, MgATP 5.0, titrated to pH 7.2 with CsOH. When the cells were kept in normal Tyrode solution, the inward sodium current elicited by depolarization to –40 mV was larger than 20 nA. Under these conditions, space and voltage control of membrane potential was unsatisfactory. To improve the clamp efficiency, we chose smaller atrial and ventricular cells, used larger suction pipettes (1–2 MΩ before series resistance compensation), and included Na$^+$ 10 mmol litre^{-1} in the Cs-pipette solution to reduce the membrane Na$^+$ concentration gradient. External Na$^+$ was reduced to 70 mmol litre^{-1} (NaCl 80 mmol litre^{-1} was replaced by *N*-methyl-D-glutamine hydrochloride). Under these conditions, if the measured I_{Na} was greater than 8 nA, time to peak I_{Na} tracings slower than 5 m or the I–V curves for I_{Na} highly skewed in shape and peaked at –40 mV (instead of –20 mV or –30 mV), the results were excluded.

Increasing concentrations of morphine (3–300 μmol litre^{-1}) were added cumulatively to the recording chamber at 10-min intervals. The inhibitory effects of morphine on I_{Na} were also tested in the presence of naloxone 10^{-7}–10^{-6} mol litre^{-1} added either 10 min before morphine or acutely during the response. To evaluate species differences, we also constructed concentration–response curves for morphine in atrial cells from human hearts. However, the mechanism of the Na$^+$-channel blocking action of morphine 10 μmol litre^{-1} was investigated only in ventricular cells from rat hearts. For measurement of I_{Ca}, contamination of I_{Na} was excluded by stepping the membrane potential to –40 mV to inactivate I_{Na}; I_{Ca} was then activated by a second step depolarization to 0 mV. During measurement of I_{to} and I_{K1}, contamination by I_{Na} and I_{Ca} was prevented by addition of tetrodotoxin 30 μmol litre^{-1} and CoCl$_2$ 1 mmol litre^{-1} to the bathing medium, respectively. The internal pipette solution contained (mmol litre^{-1}): KCl 120.0, MgCl$_2$ 5.0, MgATP 5.0, K$_2$EGTA 15.0, HEPES 10.0, titrated to pH 7.2 with KOH. Under these conditions, depolarization of membrane potentials to values positive to –40 mV from –80 mV resulted in rapid activation of I_{to} which then decayed exponentially to steady state. I_{K1} was elicited by hyperpolarization of membrane potential to values more negative than –80 mV.

DRUGS AND DATA ANALYSIS

Morphine sulphate and tetrodotoxin were purchased from Sigma Chemical Co. (St Louis, MO, USA). All values are presented as mean (SEM). Repeated-measures analysis of variance and paired Student's *t* tests were applied where appropriate, and values of $P<0.05$ were considered significant. Concentration–response curves were fitted using commercial software (SigmaPlot, Jandel) and the following Hill equation: relative values, $y=1/[1+(IC_{50}/D)^{n_H}]$, where IC_{50}=concentration for half-maximal inhibition, D=concentration of morphine and n_H=the Hill coefficient. The SigmaPlot curve fitter uses the Marquardt–Levenberg algorithm to find the coefficients (variables) of the independent variables (the *x* values) that give the best fit between the equation and the data. This algorithm seeks the values of the variables that minimize the sum of the squared differences between the observed and predicted values of the dependent variable (the *y* value). The inactivation curves of I_{Na} were fitted by the Boltzmann equation: $I/I_{max}=1/\{1+\exp[(V-V_{0.5})/s]\}$, where V=preconditioning voltage, $V_{0.5}$=voltage at which half-maximal inactivation is obtained and s=slope factor.

Results

EFFECTS ON INWARD SODIUM CURRENT (I_{Na})

Figure 1A (left) shows the time course of the inhibitory action of the sodium current by morphine 10–100 μmol litre^{-1}. Depolarizing pulses of 15 ms duration to –20 mV from a holding potential of –80 mV were applied every 5 s. Application of

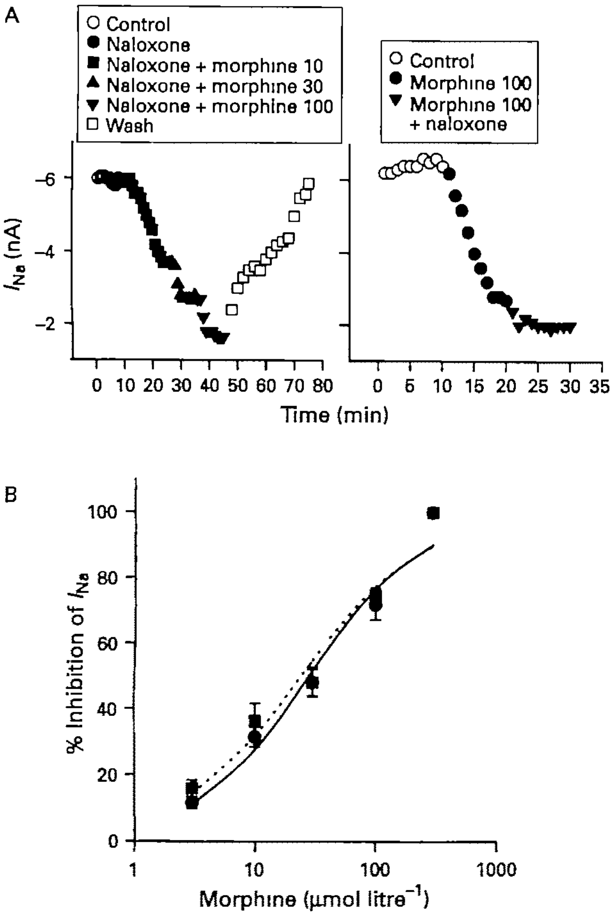

Figure 1 Effects of morphine on I_{Na}. A: Time course of the inhibitory effects of morphine 10, 30 and 100 μmol litre^{-1} in a rat ventricular cell and the effects of naloxone 0.1 μmol litre^{-1} added before (left) and after (right) morphine. B: Concentration-dependent inhibition of morphine on I_{Na} in rat ventricular (circles, n=6) and human atrial (squares, n=5) cells (mean (SEM)). Cells were stimulated at a frequency of 0.2 Hz. Current traces were recorded on 15-ms depolarizing test pulses from a holding potential of −80 mV to −20 mV.

morphine induced a dose-dependent decrease in I_{Na} and its effect reached steady state at approximately 10 min. Inhibition of I_{Na} by morphine was not prevented by pretreatment of the rat ventricular cell with an opioid receptor antagonist (naloxone 0.1 μmol litre^{-1}) or reversed by naloxone after steady-state inhibition of I_{Na} by morphine was reached (fig. 1A, right). Morphine-induced inhibition of I_{Na} was reversible after washout of morphine. Although morphine is a preferentially selective agonist for μ-opioid receptors, it can bind to σ or κ opioid receptors at concentrations greater than 0.1 μmol litre^{-1}. By blocking σ or κ opioid receptors with higher concentrations of naloxone (0.5–1 μmol litre^{-1}),[16] the possible contribution to the inhibitory action of morphine on I_{Na} via activation of these two receptors was excluded. In the presence of these concentrations of naloxone, the extent of I_{Na} inhibition was similar to that observed in cells pretreated with naloxone 0.1 μmol litre^{-1} (data not shown). The inhibitory effect of morphine on peak I_{Na} in rat ventricular myocytes was well fitted to the Hill equation. The calculated IC_{50} and n_H for morphine on I_{Na} were 30.4 (6.0) μmol litre^{-1} and 0.9 (0.1) (n=6), respectively. Similar studies in human atrial cells also found marked inhibition of I_{Na} by morphine. The average IC_{50} value for inhibition of I_{Na} in human atrial cells was calculated as 25.7 (4.5) μmol litre^{-1} (n=5). n_H for morphine in human atrial cells was 0.9 (0.1) (fig. 1B).

MODE OF INHIBITION OF I_{NA} BY MORPHINE

Figure 2A shows the representative I_{Na} recorded from a single rat ventricular cell. I_{Na} was elicited by depolarizing pulses to various test potentials (up to 50 mV) from a holding potential of −80 mV. The threshold for current activation was between −60 mV and −50 mV, and the peak current was obtained at −30 mV. Further depolarization decreased I_{Na}, with a reversal potential at approximately +50 to +60 mV. After 10-min exposure to morphine, peak I_{Na} was decreased markedly without appreciable change in the time course of the decay phase of I_{Na}. Morphine decreased the peak I_{Na} to approximately 65% of control (35% reduction). The time constant of I_{Na} inactivation determined at −20 mV in the control group was similar to that in the morphine-treated group (1.3 (0.1) ms and 1.4 (0.2) ms, respectively; n=6). Figure 2B shows the current–voltage (I–V) relationship. Morphine blocked I_{Na} without changing the threshold potential, peak potential or reversal potential.

Voltage-dependent steady-state inactivation of I_{Na} was examined by a pulse paradigm (inset in fig. 3A) in which a 15-ms test pulse to −20 mV was preceded by a 1-s preconditioning pulse to levels of −120 to −40 mV. Figure 3A shows a family of currents elicited by test pulses from different preconditioning potentials in controls, after morphine and after washout of morphine. Figure 3B shows the steady-state inactivation

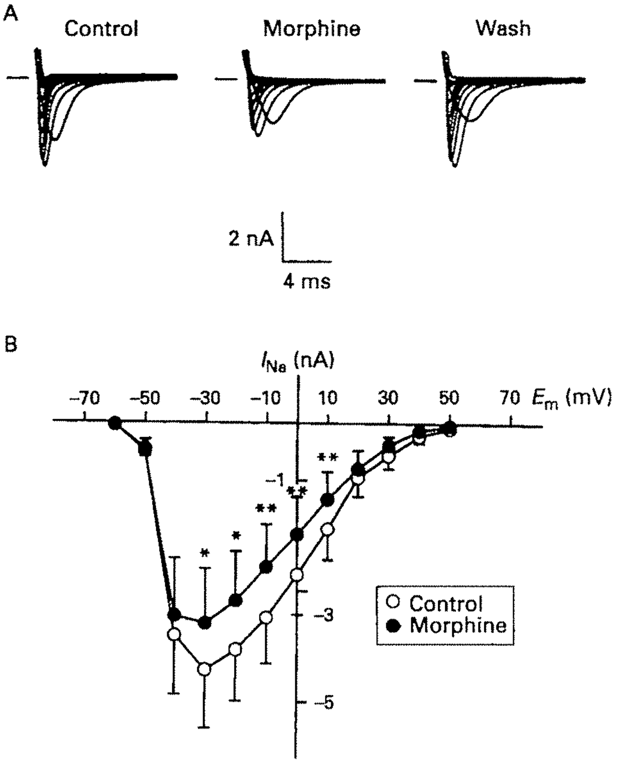

Figure 2 Effects of morphine on I_{Na} in single isolated ventricular cells from the rat. A: The original current traces elicited by depolarizing pulses applied at 10 mV increments from −60 mV to +50 mV from a holding potential of −80 mV in the absence and presence of morphine 10 μmol litre^{-1} and 10 min after washout. B: The I–V relationship for I_{Na} in the absence and presence of morphine 10 μmol litre^{-1} (mean (SEM)) *P<0.01, ** P<0.001 compared with respective controls (n=8)

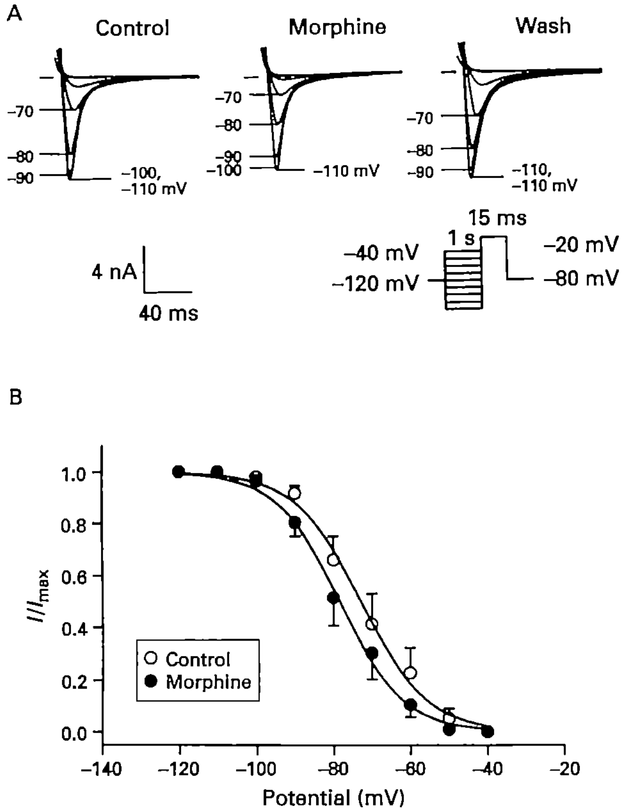

Figure 3 Effects of morphine on the steady-state inactivation curve for I_{Na}. The voltage clamp procedure is shown in the inset. A 1-s conditioning pulse was applied from a holding potential of −80 mV to various potentials ranging from −120 mV to −40 mV. Each conditioning pulse was followed by a 15-ms test pulse to −20 mV. A: The original current traces under control conditions, after application of morphine 10 µmol litre^{-1} and after washout. B: Normalized voltage-dependent steady-state inactivation curve of I_{Na} obtained before and after exposure to morphine 10 µmol litre^{-1}. I_{Na} measured at −20 mV after normalization is plotted against the conditioning potential (mean (SEM), n=10).

curves of I_{Na} from 10 experiments. $V_{0.5}$ for the steady-state inactivation curves in the controls and in the presence of morphine 10 µmol litre^{-1} were −72.2 (3.6) mV and −77.7 (3.2) mV (P<0.001 *vs* control values), respectively. The slope factors were 5.1 (0.3) mV and 5.3 (0.3) mV, respectively. This shift in the steady-state inactivation curve of I_{Na} was associated with retardation of I_{Na} recovery from inactivation.

Figure 4 shows a typical result from one cell. Recovery of I_{Na} from inactivation was studied using a two-pulse protocol (fig. 4A, inset). I_{Na} was elicited by depolarization to −20 mV and separated by intervals of 10–350 ms. Each double-pulse sequence was followed by a 5-s rest period. The time course of recovery of I_{Na}, measured in the absence and presence of morphine 10 µmol litre^{-1}, and after washout, is shown in figure 4B. The time course of I_{Na} recovery from inactivation was well fitted by two exponential equations. In controls, the time constants of the fast recovery component (τ_f) and the slow recovery component (τ_s) were 14.9 (0.5) ms and 178.9 (22.1) ms (n=5), respectively. After exposure to morphine 10 µmol litre^{-1}, the τ_f of I_{Na} was prolonged to 17.8 (0.8) ms. The τ_s of I_{Na} was, however, unaffected (169.8 (20.3) ms).

Figure 5 illustrates the effect of varying the stimulus frequency on I_{Na} block by morphine following 30 repetitive 15-ms depolarizations from a holding potential of −80 to −20 mV. The stimulation frequency varied between 0.2 and 20 Hz. As shown in figure 5, there was no use-dependent block of I_{Na} by morphine.

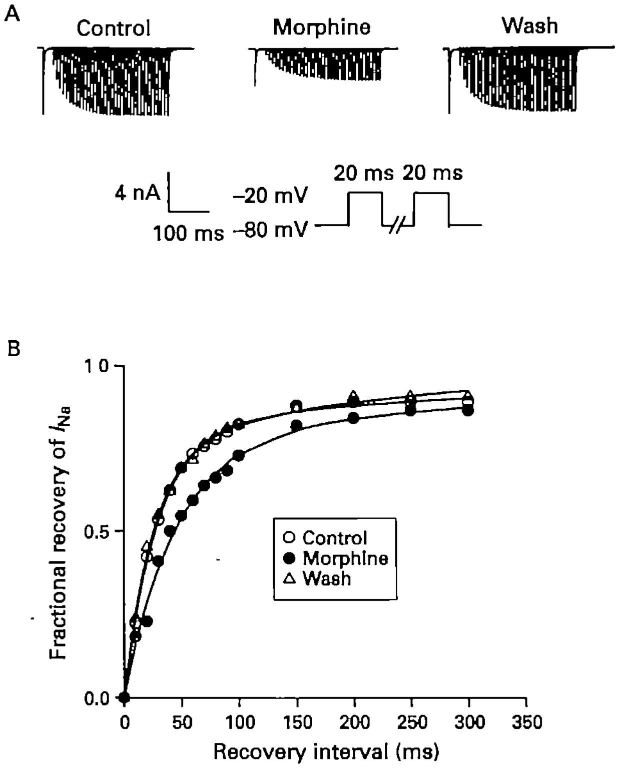

Figure 4 Effects of morphine 10 µmol litre^{-1} on recovery of I_{Na} from inactivation in rat ventricular cells. Inset shows the double pulse program. The holding potential was −80 mV. A 20-ms conditioning pulse from −80 mV to −20 mV was followed after various recovery times by a 20-ms test pulse to −20 mV. A: The original current traces under control conditions, after application of morphine 10 µmol litre^{-1} and after washout. B: Time course of recovery of I_{Na}. Test pulse current amplitude, normalized to conditioning pulse current amplitude against the recovery time in the absence and presence of morphine 10 µmol litre^{-1} and at washout. Data are from a typical experiment (n=5).

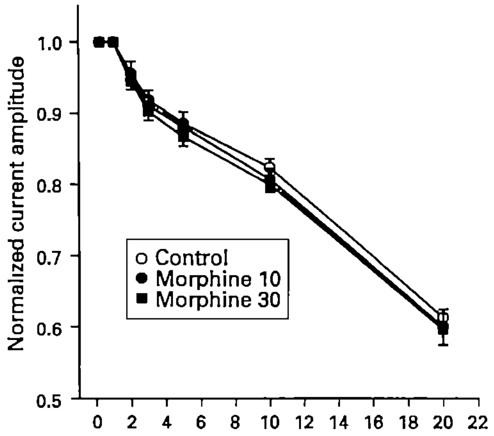

Figure 5 Effect of varying the stimulus frequency on I_{Na} by morphine 10 and 30 µmol litre^{-1}. I_{Na} was activated by depolarizing pulses to −20 mV from a holding potential of −80 mV. The 13th current traces of I_{Na} elicited by stimulation at different frequencies were normalized to the current elicited by stimulation at 0.2 Hz and plotted against stimulation frequency. Data are mean (SEM) (n=6).

EFFECT OF MORPHINE ON POTASSIUM CURRENTS AND INWARD CALCIUM CURRENT

Figure 6A (top) shows traces of K^+ currents in a rat ventricular cell elicited by depolarizing and hyperpolarizing pulses. Application of depolarizing pulses to potentials more positive than −20 mV resulted in generation of a transient outward current which then decayed to a steady-state level. On depolarization to −60, −40 and −20 mV, a constant amplitude of outward current via inward rectifying potassium channels was obtained. On hyperpolarization to potentials more negative than −80 mV, varying amplitude inward current via inwardly rectifying potassium channels was observed. Compared with inhibition of I_{Na}, the peak transient outward current, steady-state outward current and potassium current via inward rectifying potassium channels were unaffected by morphine 30 μmol litre^{-1} (fig. 6A, bottom).

Figure 6B is a typical experiment that shows the time course for the effect of morphine 30 μmol litre^{-1} on the inward calcium current (I_{Ca}) in a rat ventricular cell. These data in the presence of naloxone revealed that morphine 30 μmol litre^{-1} had no direct effect on I_{Ca}. Similar results were found in three other experiments.

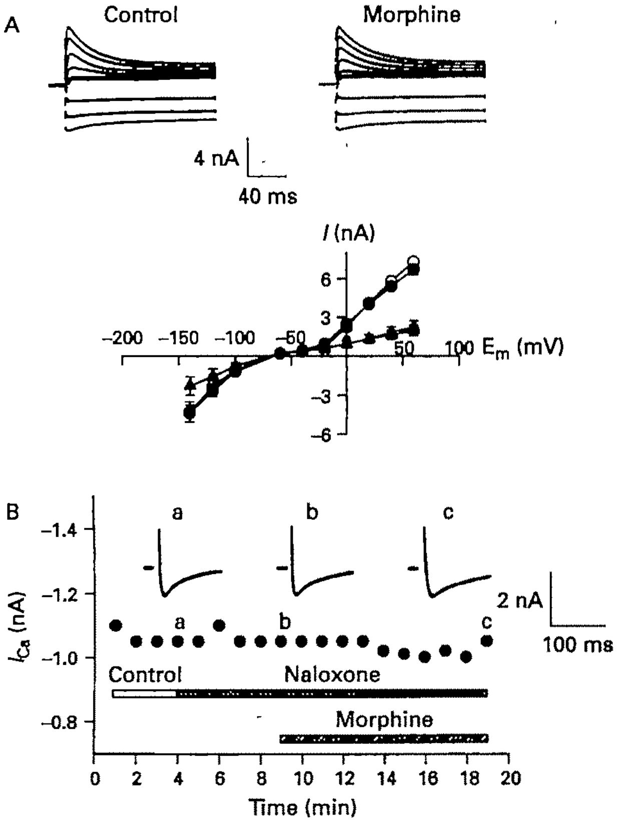

Figure 6 A: Effect of morphine on K^+ currents. Top: Families of current traces elicited by a series of 180-ms long depolarizing or hyperpolarizing pulses from a holding potential of −80 mV were obtained in the absence and presence of morphine 30 μmol litre^{-1}. Bottom: The *I–V* relationship of K^+ currents measured at the peak and end of the voltage pulses before (○, △) and after (●, ▲) exposure to morphine 30 μmol litre^{-1} (mean (SEM), n=5). B: Time course of the effects of morphine on I_{Ca}. Cells were depolarized to 0 mV from −40 mV for 120 ms. Current traces of I_{Ca} corresponding to the letters in the graph are shown in the inset.

Discussion

We have demonstrated that morphine produced reversible inhibition of I_{Na} in rat ventricular and human atrial myocytes. However, even at concentrations of up to 30 μmol litre^{-1}, morphine failed to affect Ca^{2+} and K^+ currents.

MECHANISM OF THE NA^+-CHANNEL BLOCKING ACTION OF MORPHINE

According to the results of our study, the inhibitory action of morphine on I_{Na} was not antagonized by naloxone. Thus we suggest that morphine inhibition of I_{Na} was not caused by stimulation of opioid receptors. As the extent of suppression of peak I_{Na} by morphine (fig. 2) correlated well with the negative shift of the voltage-dependent inactivation curve of I_{Na} (fig. 3) and use-dependent I_{Na} block by morphine was not observed under a higher frequency (20 Hz) of depolarization pulses, these findings suggest that morphine may inhibit I_{Na} by binding to inactivated Na^+ channels. In addition to the negative shift of the voltage-dependent inactivation of I_{Na}, retardation of the fast recovery of I_{Na} from inactivation was observed in cells treated with morphine. In spite of the retardation of fast recovery of I_{Na} from inactivation, the time constant of the slow recovery of I_{Na} from inactivation and inactivation time constant of I_{Na} remained unchanged after the cells were treated with morphine. In view of the effects on I_{Na}, the interaction of morphine with cardiac Na^+ channels can be depicted (fig. 7), where D=drug; R and O=resting and open states of the channels, respectively; and I_1 and I_2=fast and slow recovery states of inactivated channels, respectively. In the absence of drug, the major fraction of Na^+ channels in the inactivated state recovered with a fast time constant on repolarization to a holding potential of −80 mV. Therefore, most Na^+ channels exist in the I_1 state under depolarized conditions. In the presence of morphine, the time constant of the fast recovery of Na^+ channel from inactivation was increased but the time constant of the slow recovery from inactivation was unaffected; these results indicate a preferential binding of morphine to Na^+ channels in the I_1 state.

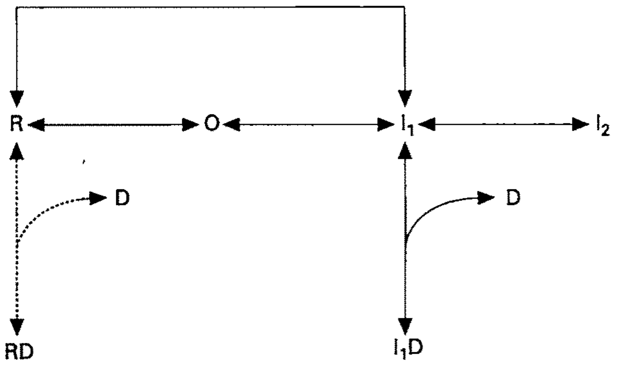

Figure 7 Interaction of morphine with cardiac Na^+ channels, where D is the drug; R and O are the resting and open states of the channels, respectively; I_1 and I_2 are the inactivated channels in fast and slow recovery states, respectively, RD is the binding of morphine to resting state channels; and I_1D is the binding of morphine to inactivated channels in fast recovery state.

As the time course of inactivation of I_{Na} at −20 mV was unchanged in the presence of morphine, the rate of transformation of Na^{+} channels from O state to I_1 state may be unaffected and binding of morphine to channels in the O state may be insignificant or not fast enough to affect the time course of I_{Na} inactivation. This consideration is further substantiated by the absence of frequency-dependent inhibition of I_{Na} by morphine (fig. 5).

According to previous studies, the potency of block of cardiac Na^{+} channels by class I antiarrhythmic agents is different when the channels exist in three different states (resting, open and inactivated states). Most class I antiarrhythmic agents have lower affinity for the channels in the resting state; their affinity increases when channels are in the open or inactivated state.[17–20] As I_{Na} elicited from a holding potential of −110 mV was reduced by morphine to a less extent than I_{Na} elicited from a holding potential of −80 mV (fig. 3A), the binding affinity of morphine to resting state Na^{+} channels may be lower than that to inactivated Na^{+} channels.

SIGNIFICANCE OF INHIBITION OF I_{NA}

In view of the insignificant direct inhibition of the inward calcium current and potassium outward current (i.e. in the presence of naloxone, fig. 6), inhibition of the inward sodium current would shorten action potential duration in some cardiac tissues, such as Purkinje fibres, in most mammalian hearts[21–23] and rat or guinea pig or human atria.[24–26] Reduction of Na^{+} influx results in less intracellular Na^{+} accumulation. Intracellular Na^{+} activity has a positive correlation with intracellular Ca^{2+} activity.[27] Lower intracellular Na^{+} activity enhances Ca^{2+} extrusion via the Na^{+}–Ca^{2+} exchange mechanism which leads to reduction of intracellular calcium and negative inotropism. Further, shorting of the action potential by inhibition of I_{Na} should decrease calcium influx via non-inactivating calcium channels.[28] This effect also contributes to negative inotropism. The 40% inhibition of I_{Na} of human atrial cells with morphine 10 μmol litre^{-1} in this study (fig. 1B) is comparable with 52% inhibition of contractile force of human atrial strips by Llobel and Laorden.[5] With regard to the antiarrhythmic activity of morphine, activation of central opioid receptor,[29] antagonism of β-adrenergic stimulation of cardiac tissues via activation of cardiac δ opioid receptor[30] and activation of cardiac K_{ATP} channels[9] were proposed as possible mechanisms responsible for the antiarrhythmic activity of morphine. In addition to these mechanisms, direct inhibition of I_{Na} by morphine may contribute partly to the antiarrhythmic activity of i.v. morphine.

In summary, morphine inhibited Na^{+} channels primarily by binding to inactivated Na^{+} channels. This effect may contribute to the negative inotropism and antiarrhythmic activity of morphine in cardiac tissues.

Acknowledgements

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References

1. Vismara LA, Leaman DL, Zelis R. The effects of morphine on venous tone in patients with acute pulmonary edema. *Circulation* 1976; **54**: 335–337.
2. Pasqualucc V, Moricca G, Solinas P. Intrathecal morphine for the control of the pain of myocardial infarction. *Anaesthesia* 1981; **36**: 68–69.
3. Laorden ML, Hernández J, Caceles MD, Miralles FS, Puig MM. Interaction between halothane and morphine on isolated heart muscle. *European Journal of Pharmacology* 1990; **175**: 285–290.
4. Micol JA, Laorden ML. Effects of μ-, δ- and κ- agonists on isolated right atria on the rat. *Neuropeptides* 1994; **26**: 365–370.
5. Llobel F, Laorden ML. Effects of morphine on atrial preparations obtained from non-failing and failing human hearts. *British Journal of Anaesthesia* 1996; **76**: 106–110.
6. Sarne Y, Flitstein A, Oppenheimer E. Anti-arrhythmic activities of opioid agonists and antagonists and their stereoisomers. *British Journal of Pharmacology* 1991; **102**: 696–698.
7. Brasch H. Influence of the optical isomer (+)- and (-)-naloxone on beating frequency, contractile force and action potentials of guinea-pig isolated cardiac preparations. *British Journal of Pharmacology* 1986; **88**: 733–740.
8. Alarcón S, Hernández J, Laorden ML. Effects of morphine: an electrophysiological study on guinea-pig papillary muscle. *Journal of Pharmacy and Pharmacology* 1992; **44**: 275–277.
9. Schultz JEJ, Hsu AK, Gross GJ. Morphine mimics the cardioprotective effect of ischemic preconditioning via the glibenclamide-sensitive mechanism in the rat heart. *Circulation Research* 1996; **78**: 1100–1104.

10 Schultz JJ, Hsu AK, Gross GJ. Ischemic preconditioning and morphine-induced cardioprotection involve the delta-opioid receptor in the intact rat heart. *Journal of Molecular and Cellular Cardiology* 1997; **29**: 2187–2195.

11. Mitra R, Morad M. A reliable method for dissociation of myocytes from heart and stomach of vertebrates. *American Journal of Physiology* 1985; **18**: H1056–H1060.
12. Su MJ, Chang YM, Chi JF, Lee SS. Thaliporphine, a positive inotropic agent with a negative chronotropic action *European Journal of Pharmacology* 1994; **254**: 141–150.
13. Escande D, Coulombe A, Faivre JF, Deroubaix E, Coraboeuf E. Two types of transient outward currents in adult human atrial cells. *American Journal of Physiology* 1987; **252**: H142–H148.
14. Chi JF, Chu SH, Lee CS, Chou NK, Su MJ. Mechanical and electrophysiological effects of 8-oxoberberine (JKL 1073A) on atrial tissue. *British Journal of Pharmacology* 1996; **118**: 503–512
15. Hamill OP, Marty A, Neher E, Sakmann B, Sigworth FJ. Improved patch clamp techniques for high resolution current recording from cells and cell-free membrane patchs. *Pflügers Archiv* 1981; **391**: 85–100.

16 Kieffer BC. Molecular aspect of opioid receptors. In. Dickenson A, Besson JM, eds. *The Pharmacology of Pain.* Berlin: Springer-Verlag, 1997, 281–304.

17. Lee KS, Hume JR, Giles W, Brown AM. Sodium current depression by lidocaine and quinidine in isolated ventricular cells. *Nature (London)* 1981; **291**: 325–327.

18 Manson JW, Hondeghem LM, Katzung BC. Amiodarone blocks inactivated cardiac sodium channels. *Pflugers Archiv* 1983; **396**: 79–81.

19. Su MJ, Lin SO, Wang CH, Tseng YZ, Tseng CD. Comparison of the electrophysiological effect of amiodarone, lidocaine and quinidine on rat ventricular cells. *Proceedings of the National Science Council, Republic of China* 1990; **14**: 105–113.
20. Koumi S, Sato R, Katori R, Hisatome I, Nagasawa K, Hajakawa H. Sodium channel states control binding and unbinding behavior of antiarrhythmic drugs in cardiac myocytes from the guinea pig. *Cardiovascular Research* 1992; **26**: 1199–1205
21. Carmeliet E, Saikawa T. Shortening of the action potential and reduction of pacemaker activity by lidocaine, quinidine, and procainamide in sheep cardiac purkinje fibers. *Circulation Research* 1982; **50**: 257–272.

22 Colatsky TJ. Mechanisms of action of lidocaine and quinidine on action potential duration in rabbit cardiac Purkinje fibers. An effect on steady state sodium currents? *Circulation Research* 1982; **50**: 17–27.

23. Sheu SS, Lederer WJ. Lidocaine's negative inotropic and antiarrhythmic action. *Circulation Research* 1985; 57: 578–590.
24. Jakob H, Nawrath H. Tetrodotoxin slightly shortens action potential duration in ventricular but not in atrial heart muscle. *Experientia* 1988; 44: 16–17.
25. Langenfeld H, Weirich J, Köhler C, Kochsiek K. Comparative analysis of the action of class I antiarrhythmic drugs (lidocaine, quinidine, and prajmaline) in rabbit atrial and ventricular myocardium. *Journal of Cardiovascular Pharmacology* 1990; 15: 338–345.
26. Ju YK, Saint DA, Gage PW. Effects of lignocaine and quinidine on the persistent sodium current in rat ventricular myocytes. *British Journal of Pharmacology* 1992; 107: 311–316.
27. Sheu SS, Fozzard HA. Transmembrane Na^+ and Ca^{2+} electrochemical gradients in cardiac muscle and their relationship to force development. *Journal of General Physiology* 1982; 80: 325–351.
28. Kass RS, Sanguinetti MC. Inactivation of calcium channel current in calf cardiac Purkinje fiber. Evidence for voltage- and calcium-mediated mechanisms. *Journal of General Physiology* 1984; 84: 705–726.
29. Rabkin SW. Morphine and morphiceptin increase the threshold for epinephrine-induced cardiac arrhythmias in the rat through mu opioid receptors. *Clinical and Experimental Physiology* 1993; 20: 95–102.
30. Xiao RP, Spurgeon HA, Capogrossi MC, Lakatta EG. Stimulation of opioid receptors on cardiac ventricular myocytes reduces L type Ca^{2+} channel current. *Journal of Molecular and Cellular Cardiology* 1993; 25: 661–666.

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Differential inhibitory effects of thiopental, thiamylal and phenobarbital on both voltage-gated calcium channels and NMDA receptors in rat hippocampal slices

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Summary

Although it is known that there are some pharmacological differences between the structurally similar barbiturates, the underlying mechanism of action remains unclear. We have compared the effects of thiopental, thiamylal and phenobarbital on both voltage-gated calcium channels (VGCC) and *N*-methyl-D-aspartate (NMDA) receptors in rat hippocampal slices by determining changes in intracellular calcium ($[Ca^{2+}]_i$). Experiments were performed in adult rat hippocampal slices perfused with Krebs solution (37°C). Concentrations of $[Ca^{2+}]_i$ in the pyramidal cell layer of the CA1 region were measured using a calcium indicator dye, fura-2. To activate VGCC and NMDA receptors, slices were exposed to K^+ 60 mmol litre^{-1} ($\leq$60 s) and NMDA 100 μmol litre^{-1} (30 s), respectively. Thiopental, thiamylal and phenobarbital were present 5 min before, during and 1 min after high K^+ or NMDA application. Both thiamylal and thiopental (50–600 μmol litre^{-1}) attenuated the increases in $[Ca^{2+}]_i$ produced by high K^+ or NMDA in a concentration-dependent manner, while phenobarbital 50–1000 μmol litre^{-1} only slightly attenuated the $[Ca^{2+}]_i$ increase produced by high K^+ at concentrations of more than 200 μmol litre^{-1} and was ineffective on the $[Ca^{2+}]_i$ response produced by NMDA. Although the increases in $[Ca^{2+}]_i$ caused by membrane depolarization with high K^+ were reduced equally with thiamylal and thiopental, thiamylal was more effective in attenuating the increase in $[Ca^{2+}]_i$ produced by NMDA receptor activation than thiopental. We conclude that the depressant effects of barbiturates on both VGCC and NMDA receptors varied between agents. Differential inhibition of both VGCC and NMDA receptors may determine the pharmacological properties of barbiturates and their ability to protect neurones against ischaemia. (*Br. J. Anaesth.* 1998; **81**: 932–939)

Keywords: hypnotics barbiturate, phenobarbital; anaesthetics i.v., thiamylal; anaesthetics i.v., thiopental; receptors, amino acid; ions, calcium; ions, ion channels, voltage-gated

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Barbiturates are central nervous system (CNS) depressants and clinically used as sedatives, hypnotics, anticonvulsants and anaesthetics. At the molecular level, all barbiturates can potentiate GABAergic neurotransmission, and this action is thought to mediate some of the behavioural changes mentioned above.[1] However, there are some pharmacological differences between the structurally similar barbiturates. For example, phenobarbital is an anticonvulsant that produces minimal sedation at clinically effective doses, whereas pentobarbital profoundly depresses the CNS at anticonvulsive doses.[2] In contrast, evidence has emerged that the ability of barbiturates to protect neurones against ischaemia varies,[3] while they all seem homogeneous in their capacity to reduce cerebral metabolic rate. Thus the GABA hypothesis does not explain the differences in pharmacological profiles of the various barbiturates. Presumably, these differences could be caused by the actions of these drugs on other target sites.

By determining intracellular calcium ($[Ca^{2+}]_i$) responses in brain slice preparations, we observed that thiopental inhibited both voltage-gated calcium channels (VGCC) and NMDA receptors and in addition, its inhibitory effect on NMDA receptors represented regional differences[4] in accordance with the regionally specific protection produced by thiopental.[5] [6] Thus we hypothesized that the inhibitory effects exhibited by each barbiturate on both VGCC and NMDA receptors may not be equivalent. In this study, we have compared the effects of three barbiturates (thiopental, thiamylal and phenobarbital) on both VGCC and NMDA receptors in rat hippocampal slices. VGCC and NMDA receptors were activated by membrane depolarization with high K^+[7] and NMDA, respectively. The activities of VGCC and NMDA receptors were determined by measuring changes in $[Ca^{2+}]_i$.[8]

Materials and methods

This study was approved by the Committee on the Guidelines for Animal Experimentation at Niigata University. Experiments were conducted on hippocampal slices obtained from male Wistar rats, weighing 100–130 g (30–35 days old). The animals were deeply anaesthetized with isoflurane and decapitated. Their brains were removed rapidly and immersed in ice-cold oxygenated Krebs solution containing (mmol litre^{-1}): NaCl 117, KCl 3.6, NaH_2PO_4 1.2, $CaCl_2$ 2.5, $MgCl_2$ 1.2, $NaHCO_3$ 25 and glucose 11.5. Brains were cut coronally into 350-μm thick sections with a vibrating tissue slicer

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(DTK-1000, Dosaka, Kyoto, Japan). Hippocampi were isolated from the appropriate sections.

To load fura-2 intracellularly, slices were incubated in oxygenated Krebs solution containing 10 μmol litre^{-1} of the acetoxymethyl ester of fura-2 (fura-2/AM) (Dojindo, Kumamoto, Japan) and 0.1% Pluronic F-127 (Boehringer, La Jolla, CA, USA) for 90 min at 21–23°C using an interface chamber. Subsequently, these slices were rinsed twice and re-incubated in oxygenated Krebs solution for an additional 20–30 min to allow hydrolysis of the acetoxymethyl ester.

The fura-2 loaded slices were transferred individually into a recording chamber (effective volume 0.30 ml) mounted on the stage of an inverted fluorescence microscope (Diaphot, Nikon, Tokyo, Japan) equipped with a 20×objective, and were superfused continuously with 95% oxygen–5% carbon dioxide-equilibrated Krebs solution. The flow rate was 5.5 ml min^{-1}, and the temperature in the recording chamber was kept at 36.5–37.5°C using a heating bath. Concentrations of $[Ca^{2+}]_i$ in the pyramidal cell layer of the CA1 region were monitored as the fluorescence of fura-2, with a microspectrofluorimeter (JASCO CAM-500, Japan Spectroscopic Co. Ltd, Tokyo, Japan), as described previously.[4 9] Excitation light was obtained from a xenon lamp (150 W) equipped with a rotating light chopper and two sets of monochromator. The intensity of fura-2 fluorescence at 510 nm emission was obtained at 340 and 380 nm excitation wavelengths. The fluorescence signals at 340 (I_{340}) and 380 nm wavelengths (I_{380}) collected from a 100 μm×400 μm area of the CA1 pyramidal cell layer with an adjustable diaphragm were detected by a photomultiplier at 1 Hz. Changes in I_{340}, I_{380} and their ratio (I_{340}/I_{380}) were recorded simultaneously with a chart writer. A true increase in $[Ca^{2+}]_i$ was identified as an increase in I_{340}/I_{380} with an increase in I_{340} but a decrease in I_{380}. Concentrations of $[Ca^{2+}]_i$ are represented as I_{340}/I_{380}.

Membrane depolarization and NMDA receptor activation were produced by exposing slices to K$^+$ 60 mmol litre^{-1} (≤60 s) and NMDA 100 μmol litre^{-1} (30 s), respectively. Tetrodotoxin 0.5 μmol litre^{-1} was present before, during and 1 min after high K$^+$ or NMDA application. Since $[Ca^{2+}]_i$ responses produced by K$^+$ 60 μmol litre^{-1} were reproducible in the same slice, changes in I_{340}/I_{380} produced by repeated exposures to K$^+$ 60 μmol litre^{-1} were normalized to the first exposure in each slice as net changes in I_{340}/I_{380}. The changes in I_{340}/I_{380} in response to NMDA were normalized to I_{340}/I_{380} just before NMDA application (peak over I_{340}/I_{380} immediately before NMDA application). To monitor the viability of slices and whether or not the effects of barbiturates were reversible, a second exposure to NMDA was performed in each slice. Data for statistical analysis were obtained from the first exposure. The effects of lanthanum (La^{3+}), a non-specific VGCC blocker,[10 11] on NMDA-mediated changes in $[Ca^{2+}]_i$ were examined in 20 mmol litre^{-1} of Hepes-buffered solution containing (mmol litre^{-1}): NaCl 123.2, KCl 3.6, NaH_2PO_4 1.2, $CaCl_2$ 2.5, $MgCl_2$ 1.2 and glucose 11.5 (pH 7.35, adjusted by NaOH).

Drugs were applied by superfusion. DL-2-amino-5-phosphonovaleric acid (APV), phenobarbital, sodium thiopental, sodium thiamylal and verapamil were added to the bathing media 5 or 10 min before, during and 1 min after high K$^+$ or NMDA application. APV, *N*-methyl-D-aspartate (NMDA), sodium thiamylal and verapamil hydrochloride were purchased from Sigma Chemical Co. (St Louis, MO, USA). Sodium thiopental was a gift of Tanabe Pharmaceutical Co. (Osaka, Japan). Lanthanum chloride, phenobarbital and tetrodotoxin (TTX) were obtained from Wako Chemical Industries Ltd (Osaka, Japan). ω-conotoxin GVIA was purchased from RBI (Natick, MA, USA), and ω-agatoxin-TK was obtained from Peptide Institute Co. (Osaka, Japan).

Data are expressed as mean (SD) and were analysed using either Student's *t* test or one-way ANOVA. ANOVA was followed by Dunnett's *post hoc* test for multiple comparisons. $P<0.05$ was considered statistically significant.

Results

CHANGES IN $[CA^{2+}]_i$ IN THE PYRAMIDAL CELL LAYER OF THE CA1 REGION IN RESPONSE TO MEMBRANE DEPOLARIZATION WITH HIGH K^+

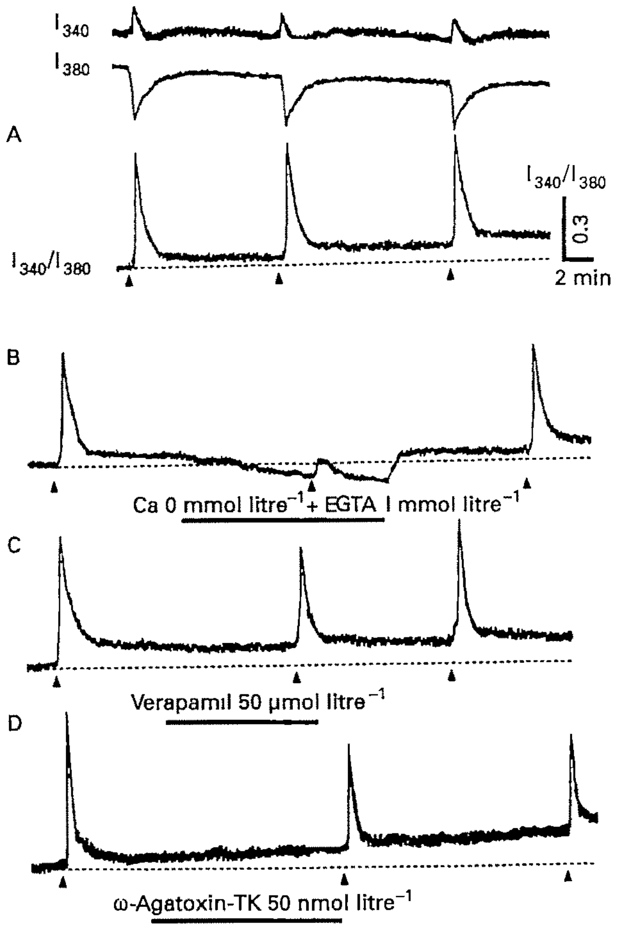

Figure 1 Original recordings showing the changes in fura-2 fluorescence signals (I_{340}) and I_{380}) and/or fluorescence ratio (I_{340}/I_{380}) in slices responding to K$^+$ 60 mmol litre^{-1} under various conditions. Experiments were performed in a $NaHCO_3$ 25 mmol litre^{-1}/carbon-dioxide- 5% buffered solution at 37.0°C The arrowheads indicate the onset of high K$^+$ The duration of high K$^+$ application was less than 60 s (removed just after the peak I_{340}/I_{380} was achieved). A: Changes in I_{340}, I_{380} and I_{340}/I_{380} when a slice was exposed repeatedly to K$^+$ 60 mmol litre^{-1}. B: Effect of Ca^{2+} removal (supplemented with EGTA 1 mmol litre^{-1}). C: Effect of verapamil 50 μmol litre^{-1}. D. Effect of ω-agatoxin-TK 50 nmol litre^{-1}. Removal of Ca^{2+} and application of Ca^{2+} channel blockers are indicated by bars below the traces. Vertical indicates net change in I_{340}/I_{380}.

Figure 1A illustrates changes in I_{340}, I_{380} and I_{340}/I_{380} when a hippocampal slice was repeatedly exposed to K^+ 60 mmol litre^{-1} for a duration of less than 60 s; the rapid increase in I_{340}/I_{380} with an anti-parallel change in I_{340} and I_{380} (increase in I_{340} but decrease in I_{380}) was reproduced in the same slice at least three times. After removal of Ca^{2+} from the bathing medium (supplemented with EGTA 1 mmol litre^{-1}), changes in I_{340}/I_{380} (normalized to the first response) by K^+ 60 mmol litre^{-1} declined to 20.1 (4.4)% (n=6) as shown in figure 1B. Perfusion of slices with ω-conotoxin-GVIA 1 μmol litre^{-1}, an N-type calcium channel blocker for 15 min, had no effect on the changes in I_{340}/I_{380} caused by K^+ 60 mmol litre^{-1} (trace not shown). Pretreatment with verapamil 50 μmol litre^{-1}, an L-type channel blocker, and ω-agatoxin-TK 50 nmol litre^{-1}, a P/Q-type channel blocker,[12 13] reduced the increases in I_{340}/I_{380} by K^+ 60 mmol litre^{-1} to 75.4 (4.3)% (n=5) and to 66.2 (2.2)% (n=4), respectively (fig. 1C–D), indicating that the increases in $[Ca^{2+}]_i$ caused by membrane depolarization with K^+ 60 mmol litre^{-1} were the result of opening of multiple Ca^{2+} channels. Inhibition of ω-agatoxin-TK was irreversible (fig. 1D).

EFFECTS OF THIOPENTAL, THIAMYLAL AND PHENOBARBITAL ON INCREASES IN $[CA^{2+}]_i$ PRODUCED BY MEMBRANE DEPOLARIZATION WITH HIGH K^+

Pretreatment with thiopental 50–600 μmol litre^{-1}, thiamylal 50–600 μmol litre^{-1} or phenobarbital 50–1000 μmol litre^{-1} did not affect either I_{340}, I_{380} or basal I_{340}/I_{380}. However, they reduced the increases in I_{340}/I_{380} caused by membrane depolarization with high K^+ in an agent-specific manner (figs 2, 3). Both thiopental and thiamylal reduced changes in I_{340}/I_{380} by K^+ 60 mmol litre^{-1} starting from a concentration of 100 μmol litre^{-1}, and their effects were maximal at 600 μmol litre^{-1}. The increases in I_{340}/I_{380} caused by K^+ 60 mmol litre^{-1} were reduced to 46.8 (3.8)% (n=7) by thiopental 100 μmol litre^{-1} and to 45.9 (6.8)% (n=6) by thiamylal 100 μmol litre^{-1}. At 600 μmol litre^{-1}, thiopental and thiamylal reduced the increases in I_{340}/I_{380} produced by K^+ 60 mmol litre^{-1} to 22.0 (3.1)% (n=6) and to 22.0 (1.6)% (n=5), respectively; both values were not significantly different from the values after removal of Ca^{2+} (20.1 (4.4)%, n=6) (unpaired t test). The increases in I_{340}/I_{380} caused by membrane depolarization with K^+ 60 mmol litre^{-1} were not affected by phenobarbital at concentrations of 50–200 μmol litre^{-1}, and were slightly reduced at concentrations greater than 200 μmol litre^{-1} (figs 2, 3).

CHARACTERISTICS OF THE NMDA-MEDIATED CHANGES IN I_{340}/I_{380} IN PYRAMIDAL CELL LAYER OF THE CA1 REGION

In the presence of Mg^{2+} 1.2 mmol litre^{-1}, exposing the slices to NMDA 100 μmol litre^{-1} for 30 s increased I_{340}/I_{380} by 134.0 (3.6)% in the CA1 pyramidal cell layer (n=6); this response was not completely reproducible in the same slice (fig. 4A). Pretreatment with APV 50 μmol litre^{-1}, a competitive NMDA receptor antagonist, reversibly abolished the NMDA-mediated increase in I_{340}/I_{380} (fig. 4B), indicating that the increase in I_{340}/I_{380} induced by NMDA initially resulted from NMDA receptor activation. As La^{3+} reacted with either HCO_3^- or $H_2PO_4^-$ to form an insoluble precipitate, its effects on the NMDA-mediated changes in I_{340}/I_{380} were examined in Hepes-buffered solution 20 mmol litre^{-1} omitting NaH_2PO_4. In the buffer solution, the increases in I_{340}/I_{380} (134.4 (4.9)%, n=6) produced by the first exposure to NMDA were not affected compared with those in the bicarbonate-buffered solution (P>0.05, unpaired t test), while the increases in I_{340}/I_{380} produced by the second exposure to NMDA usually disappeared (fig. 4C). As shown in figure 4D, the increase in I_{340}/I_{380} caused by NMDA application was not significantly reduced by adding La^{3+} 30 μmol litre^{-1} to Hepes-

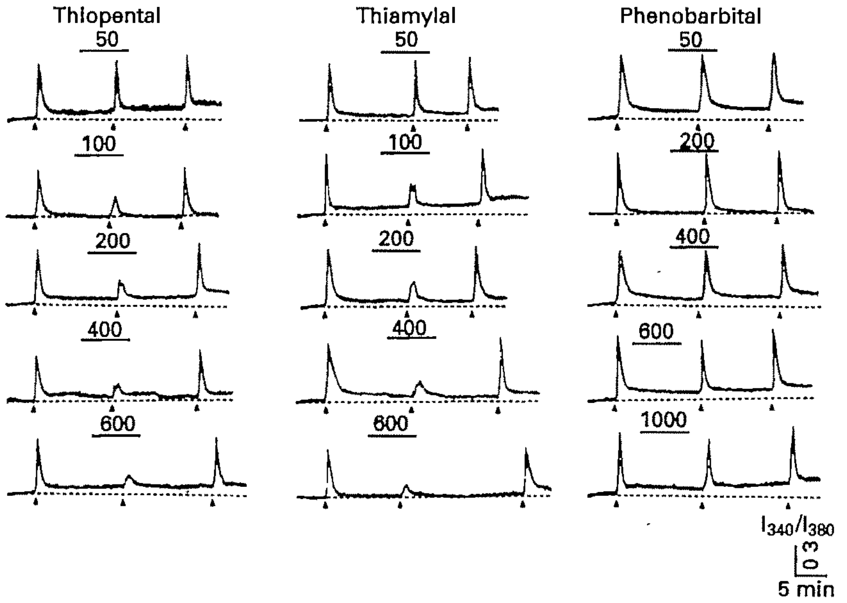

Figure 2 Effects of thiopental, thiamylal 50, 100, 200, 400 and 600 μmol litre^{-1} phenobarbital 50, 200, 400, 600 and 1000 μmol litre^{-1} on changes in I_{340}/I_{380} produced by K^+ 60 mmol litre^{-1} in the CA1 pyramidal cell layer. The arrowheads indicate the onset of high K^+. The duration of high K^+ application was less than 60 s (removed just after the peak I_{340}/I_{380} was achieved). Thiopental 50–600 μmol litre^{-1}, thiamylal 50–600 μmol litre^{-1} and phenobarbital 50–1000 μmol litre^{-1} were present 5 min before, during and 1 min after application of K^+ 60 mmol litre^{-1}, as indicated by bars above each trace. Vertical line indicates net change in I_{340}/I_{380}.

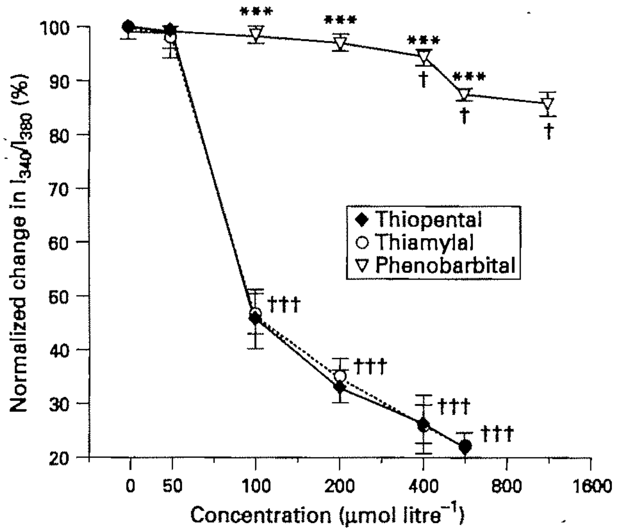

Figure 3 Concentration–response curves showing the depressant effect of thiopental, thiamylal and phenobarbital on changes in I_{340}/I_{380} produced by membrane depolarization with K^+ 60 mmol litre^{-1}. Each point represents the mean of data from 6–8 slices and vertical bars indicate SD. Statistical analyses were made by Dunnett's *post hoc* test following one-way ANOVA. ***$P<0.0001$ *vs* either thiopental or thiamylal; †$P<0.05$ *vs* zero dose; †††$P<0.0001$ *vs* zero dose.

buffered solution (131.4 (4.2)%, $n=7$). We failed to use divalent cations (cadmium or cobalt) to block VGCC in slice preparations, because these divalent cations themselves gradually changed either I_{340}, I_{380} or I_{340}/I_{380} (data not shown), probably as a result of entry of these divalent cations. The changes in I_{340}/I_{380} produced by NMDA application was essentially abolished when Ca^{2+} was removed from the bathing medium (data not shown).

EFFECTS OF THIAMYLAL, THIOPENTAL AND PHENOBARBITAL ON $[CA^{2+}]_i$ RESPONSES INDUCED BY NMDA

The increases in I_{340}/I_{380} produced by NMDA were attenuated by either thiopental 200–600 μmol litre^{-1} or thiamylal 100–600 μmol litre^{-1}. In contrast, the changes in I_{340}/I_{380} produced by the second exposure to NMDA were enhanced on increasing the concentration of thiopental or thiamylal (fig. 5). At the same concentrations, the NMDA-induced changes in $[Ca^{2+}]_i$ were attenuated to a greater extent by thiamylal compared with those by thiopental (figs 5, 7). Thiamylal produced almost complete inhibition at 200–400 μmol litre^{-1}, while complete inhibition could not be achieved by thiopental, even at 600 μmol litre^{-1}. Phenobarbital 50–1000 μmol litre^{-1} had no detectable effect on the changes in I_{340}/I_{380} produced by NMDA application (figs 6, 7) even when the duration of pretreatment was prolonged to 10 min (fig. 6).

Discussion

In brain slice preparations, the fura-2 fluorescent technique can be used to estimate the average changes in $[Ca^{2+}]_i$ of a heterogeneous population, including neuronal somata, axons and dendrites, in addition to glial cells. A true increase in $[Ca^{2+}]_i$ can be confirmed as an increase in I_{340}/I_{380} with a mirror image at I_{340} and I_{380}.[14] The principle observation in this study was that the three barbiturates (thiopental, thiamylal and phenobarbital) were differentially inhibiting the increases in $[Ca^{2+}]_i$ mediated by membrane depolarization and NMDA receptor activation.

EFFECTS OF BARBITURATES ON VOLTAGE-GATED CALCIUM CHANNELS (VGCC)

In the CNS, several classes of VGCC have been grouped according to their biophysical properties and their sensitivities to Ca^{2+}-channel blockers. Changing K^+ equilibrium potential with a high K^+ solution is the most frequently used depolarizing method, which causes the opening of VGCC without activation of sodium channels.[16] Monitoring the changes in $[Ca^{2+}]_i$ is thought to be useful for assessing the activities of VGCC during K^+ depolarization. Removal of $[Ca^{2+}]_i$ from the bathing medium reduced the high K^+-induced increases in $[Ca^{2+}]_i$ by approximately 80%, indicating that increases in $[Ca^{2+}]_i$ produced by plasma membrane depolarization with high K^+ are predominately a result of calcium entry into the cells. We did not try to compare the inhibitory effects of VGCC by the three barbiturates with other specific VGCC blockers, because there is no single agent available to eliminate the $[Ca^{2+}]_i$ response caused by larger membrane depolarization with high K^+.[17 18] However, we found that both verapamil, an L-type VGCC blocker, and ω-agatoxin-TK, a P/Q-type VGCC blocker, partially

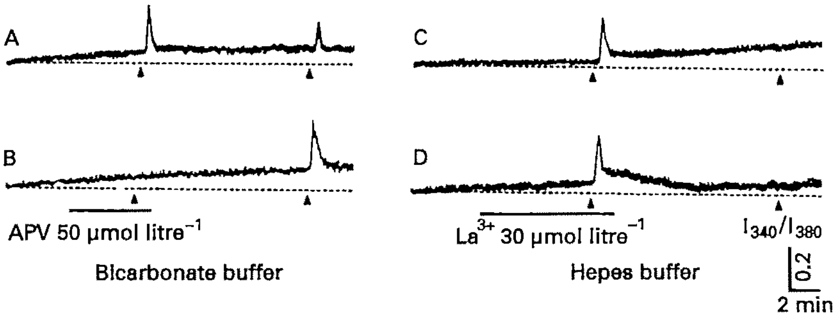

Figure 4 Typical traces showing the characteristics of the NMDA-induced changes in I_{340}/I_{380} in the CA1 pyramidal cell layer. Arrowheads indicate NMDA application (100 μmol litre^{-1} for 30 s). A: Increase in I_{340}/I_{380} caused by NMDA was not completely reproducible. B: Pretreatment with APV 50 μmol litre^{-1} (indicated by the bar beneath the trace) reversibly abolished the Ca^{2+} response produced by NMDA. C: The Ca^{2+} response to a second exposure to NMDA was almost completely abolished in the slice perfused with Hepes-buffered solution. D: In the presence of La^{3+} 30 μmol litre^{-1}, the change in I_{340}/I_{380} produced by NMDA was rarely affected. Vertical line indicates net change in I_{340}/I_{380}.

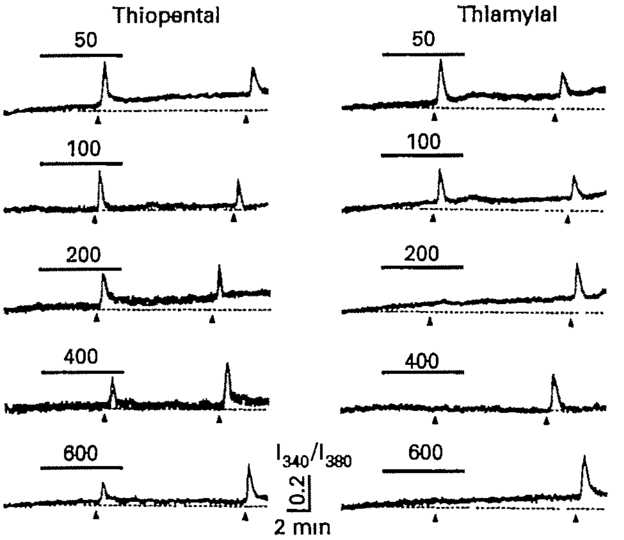

Figure 5 Effects of thiopental and thiamylal on changes in I_{340}/I_{380} caused by application of NMDA 100 µmol litre^{-1} for 30 s. Addition of NMDA is indicated by the arrowheads. Thiopental 50–600 µmol litre^{-1} and thiamylal 50–600 µmol litre^{-1} were present 5 min before, during and 1 min after exposure to NMDA, as indicated by the bars above each trace. Vertical line indicates net change in I_{340}/I_{380}.

reduced the high K$^+$-induced increases in [Ca^{2+}]$_i$. If no overlap exists between verapamil and ω-agatoxin-TK, it appears that activation of L-, P/Q-type VGCC contributes to approximately 60% of the increase in [Ca^{2+}]$_i$ produced by K$^+$ 60 mmol litre^{-1} in the CA1 pyramidal cell layer. ω-Conotoxin GVIA, an N-type calcium channel blocker, had no effect on the high K$^+$-induced increase in [Ca^{2+}]$_i$ and is consistent with the observation that ω-conotoxin GVIA is ineffective under strong depolarization.[19]

Barbiturates such as thiopental and pentobarbital are known to block calcium currents in several non-neuronal cell lines,[20–22] and in neurones.[23] By determining changes in [Ca^{2+}]$_i$, we have shown that thiopental, a typical ultra-short acting barbiturate, inhibits VGCC in a concentration-dependent manner in both the hippocampus and cortex.[4] Here we demonstrated that the inhibitory effect of thiamylal on VGCC was almost equipotent with thiopental (figs 2, 3). Comparing thiopental and thiamylal with the specific VGCC blockers, it became clear that at clinically relevant concentrations (100–400 µmol litre^{-1}), both thiopental and thiamylal were potent VGCC blockers. At 600 µmol litre^{-1}, they reduced the increases in [Ca^{2+}]$_i$ to degrees similar to removal of Ca^{2+}, suggesting that they must affect multiple VGCC. Given the importance of calcium influx through VGCC in both physiological and pathological conditions, differential inhibition of VGCCs by barbiturates might account in part for the differences in their effects on behavioural changes in addition to their neuroprotective effects.

INCREASES IN [CA^{2+}]$_i$ CAUSED BY NMDA IN THE SLICE PREPARATION

As NMDA receptor channels are highly permeable to Ca^{2+}, recording NMDA-induced [Ca^{2+}]$_i$ responses can also be used as an indicator to estimate the activities of NMDA receptors.[8] In the presence of Mg^{2+} 1.2 mmol litre^{-1}, bath-applied NMDA evoked an increase in [Ca^{2+}]$_i$ in the pyramidal cell layer of the CA1 region *in vitro*. Perfusion of slices with APV, a competitive NMDA receptor antagonist, reversibly abolished this [Ca^{2+}]$_i$ response, indicating that the [Ca^{2+}]$_i$ response initially resulted from NMDA receptor activation. Because glial cells lack NMDA receptors and their [Ca^{2+}]$_i$ concentrations are insensitive to NMDA[24], both the changes in [Ca^{2+}]$_i$ produced by NMDA receptor activation and the effects of barbiturates on these changes should be considered to occur mainly in neurones and not in glial cells. The [Ca^{2+}]$_i$ response produced by a second exposure to NMDA was smaller than that produced by the first exposure in each slice. There are two possible explanations for the gradual decline of the NMDA-mediated [Ca^{2+}]$_i$ response on repeated exposure to NMDA. First, NMDA-evoked neuronal injury[25] might result in a reduction in NMDA-mediated responses. Second, a large increase in [Ca^{2+}]$_i$ after NMDA application may lead to long-term inactivation of NMDA receptors.[26 27]

Although it is possible that the increases in [Ca^{2+}]$_i$ produced by NMDA may be in part caused by membrane depolarization after NMDA receptor activation, we did not systematically separate calcium entry through NMDA receptor-gated calcium channels or VGCC for two reasons. First, the divalent cations

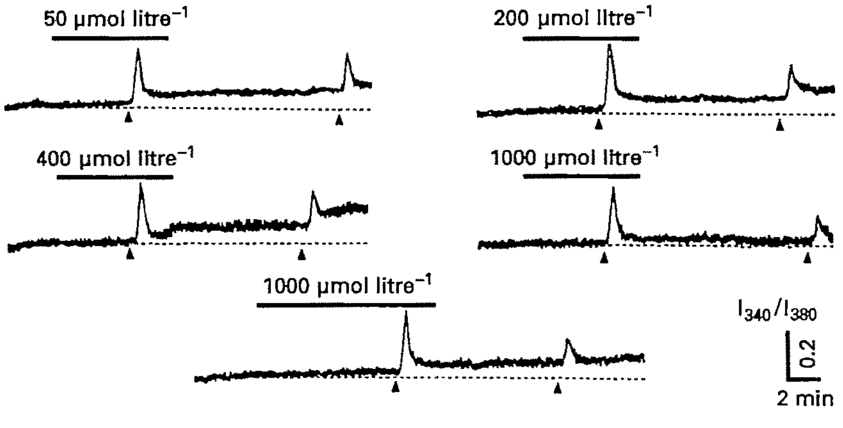

Figure 6 Original recordings showing the effects of phenobarbital on changes in I_{340}/I_{380} caused by NMDA 100 µmol litre^{-1} (30 s). Addition of NMDA is indicated by the arrowheads. Phenobarbital was present 5 min (or 10 min, bottom trace) before, during and 1 min after application of NMDA, as indicated by bars above each trace. Vertical line indicates net change in I_{340}/I_{380}.

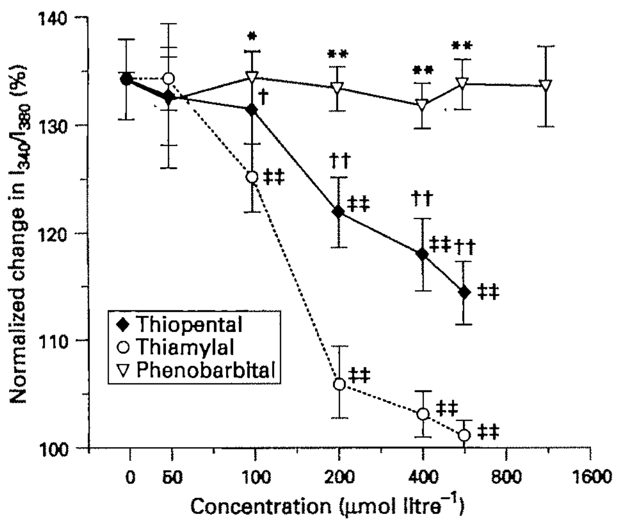

Figure 7 Concentration–response curves showing the effects of thiopental, thiamylal and phenobarbital on changes in I_{340}/I_{380} produced by application of NMDA 100 μmol litre^{-1} for 30 s. Normalization was performed by dividing peak I_{340}/I_{380} after NMDA application to I_{340}/I_{380} just before application of NMDA. Each point represents the mean of 6–8 slices and error bars indicate SD. Statistical analysis was made by Dunnett's *post hoc* test following one-way ANOVA. *P<0.05 *vs* thiamylal; **P<0 001 *vs* either thiopental or thiamylal; †P<0.01 *vs* thiamylal; ††P<0.001 *vs* thiamylal; ‡‡P<0.001 *vs* zero dose.

used to block VGCC can interact with both the calcium indicator dye fura-2 and the glutamate receptor,[8] and second, no single VGCC blocker enabled us to eliminate $[Ca^{2+}]_i$ responses caused by membrane depolarization. As described below, the changes in $[Ca^{2+}]_i$ in response to NMDA seemed to be caused mainly by opening of NMDA-gated calcium channels in the slice preparation.

DIFFERENTIAL EFFECTS OF THIOPENTAL, THIAMYLAL AND PHENOBARBITAL ON NMDA RECEPTORS

Of the three barbiturates, phenobarbital was found to be ineffective in inhibiting the $[Ca^{2+}]_i$ response produced by NMDA. Thiamylal produced almost complete inhibition at concentrations in excess of 200 μmol litre^{-1} while complete inhibition could not be achieved by increasing thiopental to 600 μmol litre^{-1}. Phenobarbital, used clinically as an anticonvulsant, did not inhibit the NMDA-induced increase in $[Ca^{2+}]_i$. This finding is consistent with the observation that the NMDA-related EPSP is not affected by phenobarbital at a concentration of 50 μg ml^{-1} (215 μmol litre^{-1}).[28] Thiamylal, an ultra-short acting barbiturate, is considered to be clinically indistinguishable from thiopental. Surprisingly, the inhibitory effect of thiamylal on NMDA receptors was more effective than thiopental. As the increases in $[Ca^{2+}]_i$ by NMDA receptor activation may in part result from opening of VGCC secondary to membrane depolarization, one can argue that the strong inhibition of the NMDA-induced $[Ca^{2+}]_i$ response by thiamylal could be related to its inhibition of VGCC. We feel that this is unlikely. First thiopental 100 μmol litre^{-1} attenuated the $[Ca^{2+}]_i$ response produced by high K^+ by more than 50% without affecting the NMDA-mediated $[Ca^{2+}]_i$ indicating that inhibiting VGCC did not simply attenuate the NMDA-mediated increase in $[Ca^{2+}]_i$. Second, La^{3+}, a non-specific VGCC blocker which has been shown to effectively attenuate kainate-mediated increases in $[Ca^{2+}]_i$ in rat dorsal horn neurones,[11] had no significant inhibition of the NMDA-mediated $[Ca^{2+}]_i$ response. Third, while the inhibition of thiamylal on the increase in $[Ca^{2+}]_i$ produced by membrane depolarization with high K^+ was almost equivalent to that of thiopental, the inhibitory effect of thiamylal on the NMDA-mediated increase in $[Ca^{2+}]_i$ was more potent than that of thiopental. These results suggest that direct inhibition of NMDA receptors, rather than inhibition of VGCC contributes to the difference between thiopental and thiamylal on NMDA-induced increases in $[Ca^{2+}]_i$. Compared with APV, a higher concentration of thiamylal was needed to completely block NMDA receptors, probably reflecting the fact that the affinity of thiamylal for NMDA receptors is lower than that of APV.

SIGNIFICANCE OF DIFFERENTIAL INHIBITION ON BOTH VGCC AND NMDA RECEPTORS BY BARBITURATES

It is interesting to note that phenobarbital, an anticonvulsive agent, only slightly attenuated the $[Ca^{2+}]_i$ response produced by membrane depolarization at concentrations greater than 200 μmol litre^{-1}. This is in accordance with the observation that inhibition of calcium current by phenobarbital is weaker than that of pentobarbital.[20] Comparison of the inhibitory effects of thiopental and thiamylal on VGCC with phenobarbital, raises the question of whether or not differential inhibition of VGCC contributes to the differences in pharmacological profiles. It is known that Ca^{2+} influx through VGCC is necessary for triggering the release of neurotransmitters[29]; one consequence of inhibition of VGCC could be block of Ca^{2+} entry into presynaptic nerve terminals and inhibition of release of neurotransmitters such as glutamate, resulting in a net reduction of excitatory synaptic transmission. Experiments performed in synaptosomes[30] and SH-SY5Y human neuroblastoma cells[31] have demonstrated that thiopental, at clinically relevant concentrations, can reduce high K^+-evoked neurotransmitter release. In addition to this, examining the interaction between VGCC blockers and anaesthetics revealed that VGCC blockers reduce, while VGCC openers increase anaesthetic requirements.[32–35] From the above observations, it is conceivable that induction of the anaesthetic state by thiopental and thiamylal may be caused partly by inhibition of VGCC. To establish that VGCC are the target sites for induction of the anaesthetic state, further efforts should be made to understand, under physiologically relevant conditions, what concentrations of barbiturates are needed to reduce Ca^{2+} entry into presynaptic terminals and the release of neurotransmitters, and whether the decreases in Ca^{2+} influx and release of neurotransmitters are causally associated in a reduction of postsynaptic membrane excitability.

Although barbiturates are known to have a protective effect against cerebral ischaemia, the underlying mechanism(s) remains unclear.[36] Evidence has emerged that combined inhibition of both VGCC and NMDA receptors may have synergistic effects in protecting ischaemic neurones; Rod and Auer[37] have shown that neither nimodipine, a VGCC blocker, nor dizocilpine, an NMDA receptor antagonist, but a combination treatment with both agents protected neurones in a rat model of transient forebrain ischaemia. On the other hand, sigma ligands, such as dextromethorphan, protect neurones against ischaemia[38 39] by a mechanism that has also been related to inhibition of both VGCC and NMDA receptors.[39 40] Thiopental has been shown to inhibit both VGCC and NMDA receptors and its inhibition of NMDA receptors is more effective in the cortex than in the hippocampus.[4] This is in good agreement with the observation that thiopental protects neurones in the cortex but not in the hippocampus.[5] On the basis of these observations, it is rational to speculate that combined inhibition on both VGCC and NMDA receptors could be important in determining the neuroprotective action of barbiturates. As the effect of thiamylal on brain ischaemia is reported rarely, experiments *in vivo* are necessary to examine if the neuroprotective effect produced by thiamylal is superior to other barbiturates, especially in the hippocampus.

In summary, the effects of barbiturates on both VGCC and NMDA receptors varied between agents. Differential inhibition of both VGCC and NMDA receptors may be factors in determining the diversity of pharmacological properties of barbiturates and their ability to protect neurones against ischaemic damage.

References

1. Sieghart W. Structure and pharmacology of gamma-aminobutyric acidA receptor subtypes. *Pharmacology Review* 1995, 47: 181–234.
2. Rogawski MA, Porter RJ. Antiepileptic drugs: pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. *Pharmacology Review* 1990; 42: 223–286.
3. Drummond JC, Cross L, Cole DJ, Patel PM. A comparison of the effect of thiopental, methohexital and pentobarbital on the extent of injury after focal cerebral ischemia in rats. *Anesthesia and Analgesia* 1998; 86: S343
4. Zhan R-Z, Fujiwara N, Endoh H, Yamakura T, Taga K, Fukuda S, Shimoji K. Thiopental inhibits increases in $[Ca^{2+}]_i$ induced by membrane depolarization, NMDA receptor activation and ischemia in rat hippocampal and cortical slices. *Anesthesiology* 1998; 89· 456–466.
5. Sano T, Dietrich WD, Drummond JC, Cole DJ. A comparison of cerebral protective effects of etomidate, thiopental and isoflurane in a model of forebrain ischemia. *Anesthesia and Analgesia* 1993; 96: 990–997.
6. Drummond JC, Cole DJ, Patel PM, Reynolds LW. Focal cerebral ischemia during anesthesia with etomidate, isoflurane, or thiopental· a comparison of the extent of cerebral injury *Neurosurgery* 1995; 37: 742–749.
7. Blaustein MP, Goldring JM. Membrane potentials in pinched-off presynaptic nerve terminals monitoring with a fluorescent probe: evidence that synaptosomes have potassium diffusion potentials. *Journal of Physiology (London)* 1975; 247: 589–615.
8. MacDermott AB, Henzi V, Reichling DB. Characterization of glutamate receptor function using calcium photometry and imaging. In: Conn PM, ed. *Methods in Neuroscience, vol. 19.* San Diego: Academic Press, 1994; 283–303.
9. Zhan R-Z, Fujiwara N, Yamakura T, Taga K, Fukuda S, Endoh H, Shimoji K. NMDA induces a biphasic change in intracellular pH in rat hippocampal slices. *Brain Research* 1997; 760: 179–186.
10. Reichling DB, MacDermott AB. Lanthanum actions on excitatory amino acid-gated currents and voltage-gated calcium current in rat dorsal horn neurons. *Journal of Physiology (London)* 1991; 441: 199–218.
11. Reichling DB, MacDermott AB. Brief calcium transients evoked by glutamate receptor agonists in rat dorsal horn neurons: Fast kinetics and mechanisms. *Journal of Physiology (London)* 1993; 469: 66–88.
12. Teramoto T, Niidome T, Miyagawa T, Nishizawa Y, Kitayama K, Sawada K. Two types of calcium channels sensitive to ω-agatoxin-TK in cultured rat hippocampal neurons. *Neuroreport* 1995; 6: 1684–1688.
13. Teramoto T, Niidome T, Kimura M, Ohgoh M, Nishizawa Y, Kitayama K, Sawada K. A novel type of calcium channel sensitive to ω-agatoxin-TK in cultured rat cerebral neurons. *Brain Research* 1997; 756: 225–230.
14. Tsien SY Fluorescence measurement and photochemical manipulation of cytosolic free calcium. *Trends in Neuroscience* 1988; 11: 419–424.
15. Tareilus E, Breer H. Presynaptic calcium channels: pharmacology and regulation. *Neurochemistry International* 1995; 26: 539–558.
16. Bernath S. Calcium-independent release of amino acid neurotransmitters: fact and artifact. *Progress in Neurobiology* 1992; 38: 57–91.
17. Kirischuk S, Voitenko N, Kostyuk P, Verkhratsky A. Calcium signalling in granule neurones studied in cerebellar slices. *Cell Calcium* 1996; 19. 59–71.
18. Perrier ML, Scatton B, Benavides J. Dihydropyridine- and omega-conotoxin-resistant, neomycin-sensitive calcium channels mediate the depolarization-induced increase in internal calcium levels in cortical slices from immature rat brain. *Journal of Pharmacology and Experimental Therapeutics* 1992; 261: 324–330
19. Dunlap K, Leubke JI, Turner TJ. Exocytotic Ca^{2+} channels in mammalian central neurons. *Trends in Neuroscience* 1995; 18. 89–98.
20. Deshumk DS, Kuizon S, Brokerhoff H. Barbiturates inhibit intracellular Ca^{2+} rise induced by thrombin in rat platelets. *Cell Calcium* 1991; 12: 645–654.
21. Park WK, Lynch C. Propofol and thiopental depression of myocardial contractility; a comparative study of mechanical and electrophysiologic effects in isolated guinea pig ventricular muscle. *Anesthesia and Analgesia* 1992; 74: 395–405.
22. Yamakage M, Hirshman CA, Croxton TL. Inhibitory effects of thiopental, ketamine, and propofol on voltage-dependent Ca^{2+} channels in porcine tracheal smooth muscle cells. *Anesthesiology* 1995; 83: 1274–1282.
23. ffrench-Mullen JMH, Barker JL, Rogawski MA. Calcium current block by (–)-pentobarbital, phenobarbital, and CHEB but not (+)-pentobarbital in acutely isolated hippocampal CA1 neurons: Comparison with effects on GABA-activated Cl^- current. *Journal of Neuroscience* 1993; 13: 3211–3221.
24. Verkhratsky A, Orkand RK, Kettenmann H. Glial calcium: homeostasis and signaling function. *Physiological Reviews* 1998; 78: 99–141
25. Zhu H, Cottrell JE, Kass I. The effect of thiopental and propofol on NMDA- and APMA-mediated glutamate excitotoxicity. *Anesthesiology* 1997; 87: 944–951.
26. Schinder AF, Montal M. Two distal modalities of NMDA receptor inactivation induced by calcium influx in cultured hippocampal neurons. *FEBS Letters* 1993; 332: 44–48.
27. Rosemund C, Feltz A, Westbrook GL. Calcium-dependent inactivation of synaptic NMDA receptors in hippocampal neurons. *Journal of Neurophysiology* 1995; 73: 427–430.
28. Ko GY-PL, Brown-Croyts LM, Teyler TJ. The effects of anticonvulsant drugs on NMDA-EPSP, AMPA-EPSP, and GABA-IPSP in the hippocampus. *Brain Research Bulletin* 1997; 42: 297–302.
29. Borst JGG, Sakmann B. Calcium influx and transmitter release in a fast CNS synapse. *Nature (London)* 1996; 383: 431–434.
30. Mantz J, Varlet C, Lecharny J-B, Henzel D, Lenot P, Desmonts J-M. Effects of volatile anesthetics, thiopental, and ketamine on spontaneous and depolarization-evoked dopamine release from striatal synaptosomes in the rat. *Anesthesiology* 1994; 80: 352–363.
31. Lambert DG, Willets JM, Atcheson R, Frost C, Smart D, Rowbotham DJ, Smith G. Effects of propofol and thiopentone on potassium- and carbachol-evoked $[^3H]$noradrenaline release and increased $[Ca^{2+}]_i$ from SH-SY5Y human neuroblastoma cells. *Biochemical Pharmacology* 1996; 51: 1613–1621.
32. Maze M, Mason DM, Ketas RE. Verapamil decreases MAC for halothane in dogs. *Anesthesiology* 1983, 59: 327–329.
33. Dolin SJ, Patch TL, Rabbani M, Taberner PV, Little HJ. Differential interaction between benzodiazepines and the dihydropyridines, nitredipine and Bay K8644. *Neuropharmacology* 1991; 30: 217–224.
34. Haorvath G, Sziszay M, Benedek G. Calcium channels are involved in the hypnotic–anesthetic action of dexmedetomidine. *Anesthesia and Analgesia* 1992; 74: 884–888.

35. Dolin SJ, Little HJ. Augmentation by calcium channel antagonists of general anaesthetic potency in mice. *British Journal of Pharmacology* 1986; **88**: 909–914.
36. Todd MM, Warner DA. A comfortable hypothesis reevaluated: cerebral metabolic depression and brain protection during ischemia. *Anesthesiology* 1992; **76**: 161–164.
37. Rod MR, Auer RN. Combination therapy with nimodipine and dizocilpine in a rat model of transient forebrain ischemia. *Stroke* 1992; **23**: 725–732.
38. George CP, Goldber MP, Choi DW, Steinberg GK. Dextromethorphan reduces neocortical ischemic neuronal damage in vivo. *Brain Research* 1988; **440**: 375–379.
39. Britton P, May Lu XC, Laskosky MS, Tortella FC Dextromethorphan protects against cerebral injury following transient, but not permanent, focal ischemia in rats. *Life Science* 1997; **60**: 1729–1737.
40. Klette KL, Lin Y, Clapp LE, Decoster MA, Moreton JE, Tortella FC. Neuroprotective sigma ligands attenuate NMDA and trans-ACPD-induced calcium signalling in rat primary neurons. *Brain Research* 1997, **756**: 231–240

British Journal of Anaesthesia 1998; **81**: 940–944

High predictive value of red cell volume measurement using carboxy-haemoglobin in a rabbit model of haemorrhage

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Summary

We have studied the accuracy of blood volume measurements using carbon monoxide (CO)-labelled haemoglobin (COHb) injection and dilution (CO method) by comparing changes in red cell volume (RCV) measured using the CO method and ^{51}Cr-labelled erythrocyte dilution (^{51}Cr method) in a haemorrhage and infusion model in rabbits. RCV was measured repeatedly using the CO method at four different blood volume stages (stages I–IV). At stages I and IV, RCV was measured simultaneously using the ^{51}Cr method. In comparing the sum of the circulating RCV and extracted RCV (SUM RCV) using the CO method, the values were almost equal and there were no significant differences between the values at the four stages. In comparing circulating RCV measured using the CO method and the ^{51}Cr method, mean difference between the two methods was 0.80 (SD 0.76) ml kg^{-1} or 4.7 (4.6)%, and a positive correlation was observed (r=0.91). We conclude that the CO method can be used to measure blood volume during perioperative periods in infants because it avoids use of a radioactive tracer, is simple and repeated measurements are possible. (*Br. J. Anaesth.* 1998; **81**: 940–944).

Keywords: measurement techniques, blood, volume; blood, volume; model, rabbit

It has been reported that haemodynamic data obtained from pulmonary artery catheters such as cardiac output and pulmonary capillary wedge pressure could not predict blood loss or erythrocyte deficit.[1] The ^{51}Cr-labelled erythrocyte dilution method (^{51}Cr method) for blood volume measurement has been reported previously.[2,3] However, the use of radioactive tracer in the operating room is prohibited and additionally, the radioactive tracer should not be injected in young patients. The indocyanine green (ICG) dilution method[4] has several problems for operative patients, and injection of dye also alters the value of the pulse oximeter in the anaesthetized patient.[5] It is reported that the carbon monoxide (CO) rebreathing method overestimates blood volume measured using the ^{51}Cr method because CO distribution in the body might be larger than true blood volume.[6]

We are now using the CO-labelled haemoglobin (COHb) injection and dilution method (CO method) for blood volume measurement. The basis of this method is the same as for ^{51}Cr. One disadvantage of the CO method is that a volume of more than 50 ml of CO-labelled blood is necessary to obtain reliable data in adult patients.[7] However, the CO method has several advantages over other methods because it requires only a brief time for labelling and allows rapid and repeated measurements with a CO-oximeter in the operating room or intensive care unit (ICU). Further, the CO method avoids use of a radioactive tracer and could be used to measure blood volume in children.

In this study, we have investigated the accuracy and reliability of the CO method in a haemorrhage and infusion model using rabbits. The accuracy of blood volume measurement was determined by assessing changes in red cell volume (RCV) at four different blood volume stages and then comparing the values measured using the CO method with those obtained with the ^{51}Cr method. Rabbits were used because body weight is similar to human infants. Demonstration of the accuracy and reliability of the CO method may indicate the clinical usefulness of this technique in blood volume measurement in infants.

Materials and methods

ANIMAL PREPARATION

The experimental procedure was approved by the Animal Care and Use Committee of Gunma University. Six Japanese white male rabbits weighing 2.3–3.7 (3.1±0.6) kg were used. Before the study, rabbits were anaesthetized with 1–4% sevoflurane and oxygen via a face mask to enable catheterization. A 3-French gauge catheter was inserted into the jugular vein for fluid infusion and for injection of CO-labelled blood or ^{51}Cr -labelled erythrocytes. For blood sampling and withdrawal, another 3-French gauge catheter was inserted into the carotid artery. Arterial pressure and heart rate were monitored using an arterial pressure monitoring system (AP601G, Nihon-Kohden, Tokyo, Japan) connected to the carotid arterial catheter. After placement of the catheters, rabbits were allowed to recover from

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anaesthesia and were then restrained in a standard stainless-steel rabbit holder in room air.

PROCEDURE FOR MEASUREMENT OF RCV

CO method

RCV was measured in four stages: normovolaemic stage (stage I); removal of blood (stage II); after infusion of physiological saline and hydroxyethylstarch (HES) (stage III); and after re-transfusion of the blood removed before stage II (stage IV).

At stage I, 4.5 ml of blood were obtained into a syringe containing heparin sodium solution. After measurement of haematocrit, 4 ml of blood were labelled by mixing with CO gas for 10 min in a 20-ml syringe. The mean COHb concentration in the CO-labelled blood was higher than 95% when mixing was completed, and remained at this concentration for more than 5 h in the syringe. COHb concentrations were measured using a CO-oximeter (OSM3, Radiometer, Copenhagen, Denmark) adjusted in the animal mode for rabbit haemoglobin. Arterial blood-gas tensions were measured simultaneously (ABL300, Radiometer, Copenhagen, Denmark).

After obtaining two 0.5-ml samples of blood for measurement of baseline COHb concentration, 3 ml of CO-labelled blood were injected into the venous catheter. After injection of CO-labelled blood, two 0.5-ml samples of blood were obtained at 4, 8 and 12 min (fig. 1).

In our preliminary experiment, blood sampling for measurements of COHb concentration was performed at 2, 4, 8, 12, 16 and 32 min after injection of CO-labelled blood. However, the values at 2 min varied widely and were not considered for estimation of blood volume. The COHb regression line was stable for 4–12 min in rabbits (fig. 2) which has also been reported in dogs.[7] Therefore, values at 4, 8 and 12 min were used for calculation of RCV in this study.

After injection of CO-labelled blood, several distinct dilutional phases are observed: an early circulation and intravascular mixing phase and a major dilution phase.[8] In this study, a major dilution phase was achieved within 4 min, and its exponential decay was used for estimation of RCV circulating in the body. Therefore, the logarithms of this phase were extrapolated by the method of least squares to the time of injection of CO-labelled blood. Circulating RCV was calculated from the following equation:

$$V_i\,(\text{ml})\times \text{Ht}_i\,(\%)\times \text{COHb}_i\,(\%)=\text{BV}_c\,(\text{ml})\times \text{Ht}_a\,(\%)\times(\text{COHb}_e - \text{COHb}_b)\,(\%)$$

$$\text{RCV}_c\,(\text{ml})=\text{BV}_c\,(\text{ml})\times 0.9\times \text{Ht}_b\,(\%)\div 100$$

where V_i=injected volume of CO-labelled blood; Ht_i, COHb_i=haematocrit and COHb concentration in CO-labelled blood; Ht_a=haematocrit after injection of CO-labelled blood; Ht_b, COHb_b=haematocrit and COHb concentration in circulating blood before injection of CO-labelled blood; COHb_e=extrapolated COHb concentration in circulating blood at the time of injection of CO-labelled blood; and RCV_c and BV_c=circulating red cell volume and circulating blood volume, respectively.

The haematocrit of each sample was determined in duplicate using the micromethod. Capillary tubes were centrifuged for 5 min at 12 000 rpm. The difference between peripheral and central haematocrit, which is termed an F cell ratio, influences calculation of blood volume. Whole-body haematocrit (Ht-b), obtained from direct measurement of RCV and plasma volume, is consistently lower than venous haematocrit (Ht-v). The ratio of Ht-b/Ht-v was reported to be approximately 0.9.[2] Therefore, we used an F cell ratio of 0.9 in this study.

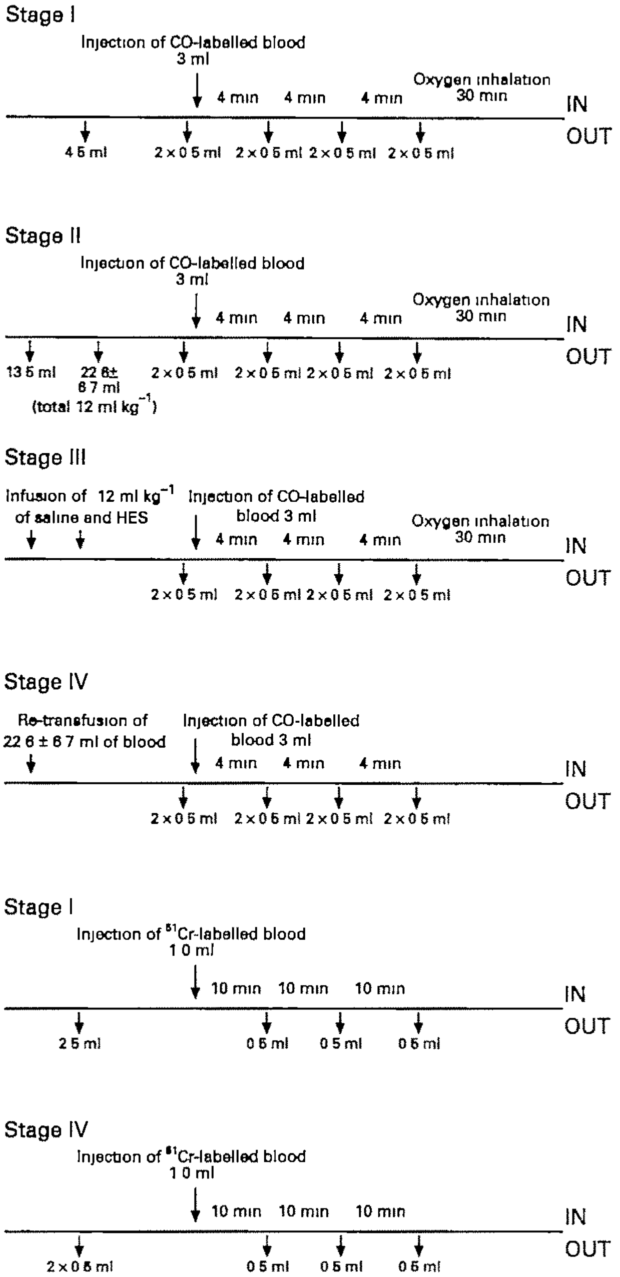

Figure 1 Procedures for measurement of red cell volume using the CO (stages I, II, III and IV) and ^{51}Cr (stages I and IV) methods. HES=Hydroxyethylstarch.

As shown in figure 1, after measurement at stage I, 13.5 ml of blood were obtained for CO-labelling which was used for measurements of blood volume at stages II, III and IV (4.5 ml for each measurement). In order to induce the hypovolaemic stage (stage II), another 22.6±6.7 ml of arterial blood were then obtained, giving a total volume of blood removed of 12 ml kg^{-1}. At stages II, III and IV, RCV was measured using the same method as that used at stage I. At stage III, RCV was measured after infusion of physiological saline 12 ml kg^{-1} and HES 12 ml kg^{-1}.

At stage IV, RCV was measured after re-transfusion of the previously removed blood (22.6±6.7 ml).

After each measurement, pure oxygen was administered via a face mask for 30 min to facilitate dissociation of CO from haemoglobin. Baseline COHb concentrations before injection of CO-labelled blood were less than 2.5% at each stage.

The ^{51}Cr method

RCV was measured using the ^{51}Cr method[2] in stages I and IV at the same time as measurements using the CO method. Initially, 2.5 ml of blood were obtained and labelled with ^{51}Cr. After centrifugation and washing in physiological saline, ^{51}Cr-labelled erythrocytes were suspended in physiological saline. Haematocrit and ^{51}Cr radioactivity were measured with 0.5 ml of this suspension. After injection of 1 ml of the ^{51}Cr-labelled erythrocyte suspension, 0.5 ml of blood were obtained at 10, 20 and 30 min for measurement of ^{51}Cr radioactivity in circulating blood (fig. 1). Another 1 ml of ^{51}Cr-labelled erythrocyte suspension was used for measurement at stage IV. At stage IV, before injection of ^{51}Cr-labelled erythrocyte suspension, two 0.5-ml samples of blood were obtained for measurement of baseline ^{51}Cr radioactivity in circulating blood as an indication of residual ^{51}Cr radioactivity used at stage I.

In these measurements, haematocrit of all blood obtained was measured for calculation of SUM RCV and extracted RCV (RCV_e). SUM RCV and RCV_e were defined as follows.

$$\text{SUM RCV} = RCV_c + RCV_e$$

where RCV_e=sum of the RCV removed to induce the hypovolaemic stage and RCV for labelling and sampling which existed extracorporeally at each measurement.

STATISTICAL ANALYSIS

Data are presented as mean (SD). One-way analysis of variance followed by Scheffé's *F* test was performed to compare differences between individual measurement data. $P<0.05$ was considered statistically significant.

Results

HAEMODYNAMIC OBSERVATIONS

Mean arterial pressure in stage I was 106 (12.5) mm Hg, which decreased significantly to 79 (15.0) mm Hg, 85.8 (14.8) mm Hg and 91 (11.5) mm Hg during stages II, III and IV, respectively.

CHANGES IN HAEMATOCRIT

Haematocrit before measurement of stage I was 41.8 (2.5)%. Haematocrit of CO-labelled blood for measurements of stages II, III and IV was 40.3 (2.6)%. Haematocrit before measurements during stages II, III and IV were 36.2 (1.4)%, 27.5 (2.2)% and 33.4 (1.7)%, respectively.

COHB AND ^{51}CR CONCENTRATIONS

Mean COHb concentration of CO-labelled blood during all four stages was 97.0 (1.1)%. Figure 2 shows COHb concentrations of circulating blood in four measurements after injection of 3 ml of CO-labelled blood.

Using the ^{51}Cr method, mean ^{51}Cr radioactivity after injection of ^{51}Cr-labelled erythrocyte suspension in circulating blood in stage IV (5786 (757) counts) was approximately 1.7 times higher than that in stage I (3341 (526) counts).

RED CELL VOLUME AND RELATIONSHIP BETWEEN THE TWO METHODS

Table 1 shows RCV_c, RCV_e and SUM RCV at each measurement. In the CO method, there were no significant differences in the values of SUM RCV between the four stages. There were no significant differences between the values measured using the CO and ^{51}Cr methods at stages I and IV. Figure 3 shows the correlation between the RCV_c values of the two methods and the regression line ($Y=0.99X+0.9$, $r=0.91$). Figure 4 shows the difference in paired RCV_c measured using the two methods. The mean of the difference was 0.80 (0.76) ml kg^{-1} and the mean of the percent difference was 4.7 (4.6)%, respectively.

After completion of the experiments, all rabbits were released from the rabbit holder and survived for more than 3 months without complication.

Discussion

In this study, we have demonstrated the accuracy of blood volume measurement using CO-labelled blood in rabbits. The values of SUM RCV measured using the CO method in all four stages were similar and a positive correlation ($r=0.91$) (fig. 3) was observed between the values of RCV_c measured by the CO and ^{51}Cr methods. The CO method overestimated 0.8 ml kg^{-1} or 4.7% of the ^{51}Cr method (fig. 4), indicating no clinically significant bias. In blood volume measurement, we do not know of any reports similar to ours which have compared the differences before and after haemorrhage using two different methods.

Previously studied blood volume measurements using CO were performed mainly by CO inhalation. Nomof and colleagues[6] reported that RCV measured using the CO-rebreathing method was 16% larger

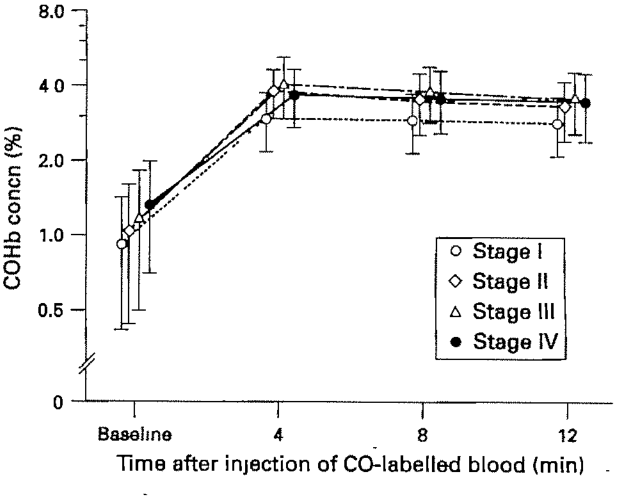

Figure 2 Changes in COHb concentrations in circulating blood after injection of 3 ml of CO-labelled blood during the four stages noted in figure 1. Data are mean (SD).

Table 1 Circulating red cell volume (RCV_c), extracted red cell volume (RCV_e) and sum of RCV_c and RCV_e (SUM RCV) in the four stages described in figure 1. Data are mean (SD). *$P<0.05$ compared with stage I measured using the CO method

	CO method				^{51}Cr method	
	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage IV
RCV_c (ml kg^{-1})	19.1 (0.7)	13.3 (0.7)*	13.0 (1.0)*	15.8 (0.9)*	18.2 (0.7)	15.1 (0.8)
RCV_e (ml kg^{-1})	0.37 (0.7)	5.1 (0.2)*	5.1 (0.7)*	2.5 (0.4)*	0.37 (0.7)	2.5 (0.4)
SUM RCV (ml kg^{-1})	19.4 (0.7)	18.4 (0.7)	18.2 (1.0)	18.3 (1.0)	18.6 (0.8)	17.6 (0.9)

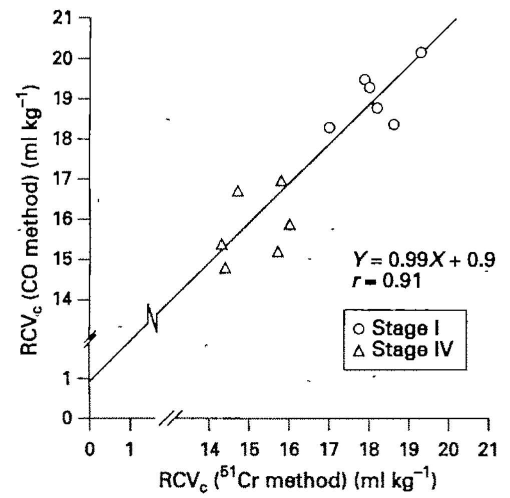

Figure 3 Relationship between circulating red cell volume (RCV_c) measured using the CO and ^{51}Cr methods. Each point represents RCV_c of six rabbits measured at stages I and IV, as noted in figure 1.

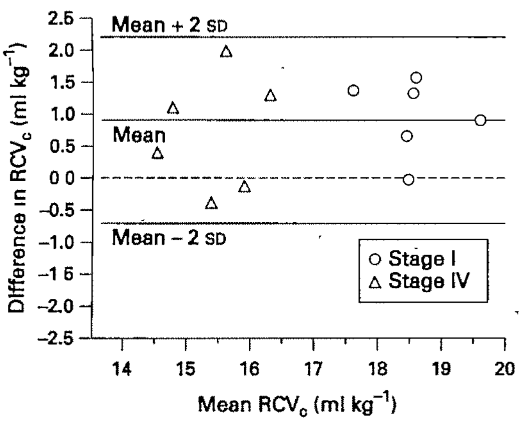

Figure 4 Difference in circulating red cell volume (RCV_c) measured using the CO and ^{51}Cr methods plotted against their respective means. Each point represents RCV_c of six rabbits measured at stages I and IV, as noted in figure 1. The horizontal lines indicate mean (2 SD). The mean of the difference was 0.80 (SD 0.76) ml kg^{-1}.

than that of the ^{51}Cr method, as some CO was located in the extravascular space and some was excreted, metabolized or leaked. Root, Allen and Gregersen[9] reported that RCV measured using COHb injection and dilution was 12% greater than that of the ^{32}P-labelled method. Fukui and Shigemi[7] reported that the ratio of blood volume values assessed by COHb injection and dilution relative to the ^{51}Cr method ranged from 0.86 to 1.17, with a mean ratio of 1.0±0.1 (r=0.93). In our study, the ratio of RCV_c values by the CO method to the ^{51}Cr method ranged from 0.97 to 1.14, with a mean ratio of 1.05 (0.05) (r=0.91); the CO method slightly overestimated the ^{51}Cr method. One possible explanation for overestimation of the CO method is that a small amount of CO is released from haemoglobin and lost into plasma immediately after injection. Because in CO-labelled blood the plasma is saturated with CO, CO in plasma is diluted by circulating plasma and extracellular fluid when injected into the systemic circulation. The rapid decrease in COHb volume on injection may be responsible for overestimation of blood volume.

In this study, actual blood loss between stages I and II was 12 ml kg^{-1}. However, loss of circulating blood volume calculated by the CO method was 10.2 (2.0) ml kg^{-1} (circulating blood volume values in stages I and II were 51.1 (3.7) ml kg^{-1} and 40.9 (2.3) ml kg^{-1}, respectively). The difference in these values may be explained by the influx of extravascular fluid into the systemic circulation because the haematocrit at stage II decreased compared with that at stage I. Circulating blood volume is changed by extracellular fluid movement and infusion and therefore we compared the values of SUM RCV at four different blood volume stages for determining the accuracy of the CO method. If there was no unaccountable blood loss, SUM RCV should maintain at a constant value at each stage. However, the percent differences of SUM RCV between stage I and stages II, III and IV gradually increased and reached a maximum value of 6.0% at stage IV (the mean of the difference between stages I and IV was 1.2 (0.4) ml kg^{-1}). These small increases may be caused in part by unaccountable blood loss, such as bleeding from the surgical region, and blood loss during labelling and sampling.

In our preliminary experiment, we measured blood volume using the CO method without oxygen inhalation after each measurement. Baseline COHb concentrations in circulating blood at each stage increased gradually with repeated measurements. These increased baseline values generated a larger deviation in blood volume data and therefore we administered pure oxygen for 30 min after each measurement. Baseline COHb concentrations in the four measurements were within 0.4–2.4% in this study. These data suggest that oxygen inhalation is necessary before repeated measurements using the CO method. Pure oxygen inhalation rapidly decreased blood COHb concentrations. In contrast, ^{51}Cr radioactivity in circulating blood in stage IV was approximately 1.7 times higher than that in stage I.

In a recent study, Fogh-Andersen and colleagues[10] observed that the absorption spectrum of COHb, using an OSM3 analyser, depended on pH and $P\text{CO}_2$. To minimize this error, we included 5% CO in the calibration gas mixture for the two-point calibration of the OSM3 analyser. Pa_{CO_2} in rabbits was maintained at 4.0–4.7 kPa throughout the experiment.

There are some disadvantages in the tracer dilution methods. It has been reported that the initial major dilution is achieved within 10–20 min in humans but is prolonged by circulatory dysfunction.[8] In dogs, the major dilution phase was achieved within 10 min[7] because the phase may be shorter than in humans because of smaller body size, smaller blood volume and higher heart rate. As it was shown that the dilution phase was achieved within 4 min in rabbits in our study, RCV was calculated from the data obtained at 4, 8 and 12 min after injection of CO-labelled blood.

Using our method, the toxicity of CO-labelled blood should be considered. COHb concentration in circulating blood was lower than 6% after injection of CO-labelled blood in all rabbits. A higher concentration of COHb is sometimes observed in smokers with no symptoms and is harmless in humans when the concentration is less than 10%.[7 11 12] All rabbits in this study survived for more than 3 months without complications after completion of the experiments.

Several methods for blood volume measurement have been reported recently. Sugimoto and colleagues[3] reported a method for continuous measurement of blood volume using ^{51}Cr in rats. Throughout their experiment there was no change in erythrocyte volume and therefore changes in blood volume were calculated continuously from changes in the radioactivity of ^{51}Cr in circulating blood. If there is bleeding, their method could not be used to calculate blood volume. Hoeft and colleagues[4] reported a different method for measuring blood volume using ICG. However, blood ICG concentration is influenced by hepatic clearance, distribution of ICG, cardiac output and circulation time. A two-compartment model of the circulation is required for an adequate fit of the data. Abdominal surgery also changes splanchnic blood flow, and therefore measurement of blood volume using ICG may have some disadvantages during anaesthesia and surgery.[13] Christensen, Rasmussen and Henneberg[14] reported on the CO-rebreathing method using a to and fro system, and analysed CO kinetics by computer simulation. This method is useful for patients who are treated in the intensive care unit. They used a special system designed by Water's Co. to avoid CO leakage. However, in the operating room it is difficult to use these types of instruments during surgery. In our method, special instruments and computer analysis were not necessary. Moreover, CO labelling, blood sampling, COHb measurements and blood volume calculation are completed within 30 min in the operating room. The CO method has advantages, especially for young patients, because it avoids the use of a radioactive tracer, and injection of CO-labelled blood was shown to be safe.

In summary, we have demonstrated the highly predictive value of RCV using a small volume of CO-labelled blood in rabbits. This method may be useful for repeated measurements of blood volume during the perioperative period in infants.

References

1. Cordts PR, LaMorte WW, Fisher JB, DelGuercio C, Niehoff J, Pivacek LE, Dennis RC, Siebens H, Georgio A, Valeri CR, Menzoian JO. Poor predictive value of hematocrit and hemodynamic parameters for erythrocyte deficits after extensive elective vascular operations. *Surgery, Gynecology and Obstetrics* 1992; **175**: 243–248.
2. A report by the International Committee for Standardization in Hematology (ICSH): Panel on diagnostic applications of radioisotopes in haematology. Standard techniques for the measurement of red-cell and plasma volume. *British Journal of Haematology* 1973; **25**: 801–814.
3. Sugimoto E, Shigemi K, Okuno T, Yawata T, Morimoto T. Effect of ANP on circulating blood volume. *American Journal of Physiology* 1989; **257**: R127–R131.
4. Hoeft A, Schorn B, Weyland A, Scholz M, Buhre W, Stepanek E, Allen SJ, Sonntag H. Bedside assessment of intravascular volume status in patients undergoing coronary bypass surgery. *Anesthesiology* 1994; **81**: 76–86.
5. Scheller MS, Unger RJ, Kelner MJ. Effects of intravenously administered dyes on pulse oximetry readings. *Anesthesiology* 1986; **65**: 550–552.
6. Nomof N, Hopper J jr, Brown E, Scott K, Wennesland R Simultaneous determinations of the total volume of red blood cells by use of carbon monoxide and chromium^{51} in healthy and diseased human subjects. *Journal of Clinical Investigation* 1954; **33**: 1382–1387.
7. Fukui M, Shigemi K. Determination of single and repeated red cell volumes by the indicator dilution method using carbon monoxide as the indicator. *Critical Care Medicine* 1989; **17**: 1199–1202.
8. Moore FD, Hartsuck JM, Zollinger RM, Johnson JE. Reference models for clinical studies by isotope dilution. *Annals of Surgery* 1968; **168**: 671–700.
9. Root WS, Allen TH, Gregersen MI. Simultaneous determinations in splenectomized dogs of cell volume with CO and P^{32} and plasma volume with T-1824. *American Journal of Physiology* 1953; **175**: 233–235.
10. Fogh-Andersen N, Thomsen JK, Foldager K, Siggaard-Andersen pH effect on the hemoglobin carbon monoxide absorption spectrum: Importance for calibration of the OSM3 and measurement of circulating hemoglobin and blood volume. *Scandinavian Journal of Clinical and Laboratory Investigation* 1990; **50**. (Suppl. 203): 247–252.
11. Okada Y, Tyuma I, Ueda Y, Sugimoto T. Effect of carbon monoxide on equilibrium between oxygen and hemoglobin. *American Journal of Physiology* 1976; **230**. 471–475.
12. Hlastala MP, McKenna HP, Franada RL, Detter JC. Influence of carbon monoxide on hemoglobin–oxygen binding. *Journal of Applied Physiology* 1976; **41**: 893–899.
13. Henthorn TK, Avram MJ, Krejcie TC, Shanks CA, Asada A, Kaczynski DA. Minimal compartmental model of circulatory mixing of indocyanine greeen. *American Journal of Physiology* 1992; **262**: H903–H910.
14. Christensen P, Rasmussen JW, Henneberg SW. Accuracy of a new bedside method for estimation of circulating blood volume. *Critical Care Medicine* 1993; **21**. 1535–1540.

British Journal of Anaesthesia 1998; **81**: 945–956

REVIEW ARTICLE

Pulmonary artery catheterization in anaesthesia and intensive care

C. M. H. GÓMEZ AND M. G. A. PALAZZO

Since its introduction nearly 30 yr ago, the pulmonary artery catheter (PAC) has become part of everyday management in cardiology, anaesthesia and intensive care but remains controversial.[12,37,78,136,164] The apparent failure to demonstrate improvements in patient outcome[28,66,68,192] and the risks associated with its use[15,153] have long been criticized.[139] Failure to explore its full use and redundancy of the catheter after initial placement are additional concerns. More worrying is the incorrect interpretation of data [64,82,97] and consequent misdirection of therapy. Others are disturbed by a reliance on measurements rather than on clinical signs.[140] However, many argue that the PAC enhances bedside understanding of cardiorespiratory interactions, complements the interpretation of clinical signs and benefits management of haemodynamic disorders.[47,53,62,65,77,136,157,170]

The first part of this article reviews the history, technical aspects and practical uses of pulmonary artery catheterization. The second part evaluates the clinical impact of the PAC on anaesthesia and intensive care medicine.

Historical developments

A century and a half ago Bernard, and later Chauveau and Marey, detailed left and right heart catheterization in live animals while studying pulmonary "combustion" (heat production)[6] and the timing of the apical beat.[23]

In 1929, Forssmann catheterized his own right atrium.[55] The following year Jiménez Díaz and Sánchez Cuenca reported the first series of patients to undergo right atrial catheterization.[88] Cardiac output by the Fick method was validated over the following decade, initially sampling from the right atrium but quickly progressing to the pulmonary artery.[34,94] Forssmann, Cournand and Richards shared the 1956 Nobel prize in medicine and physiology.

Pulmonary artery occlusion (without a balloon) was first reported in 1947 for oxygen measurement[42] and in 1948 and 1949 for pressure measurement.[75,99] In 1953, pulmonary artery occlusion with a balloon-tipped, flow-directed catheter was pioneered in dogs.[101]

In 1964, Bradley described the use of the PAC at the bedside[17] and 4 yr later Branthwaite validated thermodilution cardiac output measurement in humans.[18,50] Seventeen years after its first description in dogs, Swan and colleagues described pulmonary artery occlusion with a balloon-tipped, flow-directed catheter in humans.[169]

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Keywords: equipment, catheters pulmonary artery; intensive care; heart, myocardial funcion; cardiorespiratory system, effects

Practical considerations

INSERTION

Usually the PAC is inserted into a central vein through a large (7.5–9 F) percutaneous sheath. The internal jugular vein is the preferred site of cannulation, with a low risk of pneumothorax. The incidence of carotid artery puncture is 1.5–2% and its inadvertent cannulation is less than 1 in 1000. The subclavian route has a higher risk of pneumothorax and arterial puncture whereas the femoral vein may be a difficult site from which to float the catheter.[90,118,153]

If difficulty in distinguishing venous from arterial puncture is anticipated, the vessel can be entered with a small cannula before percutaneous dilatation; a typical venous waveform after connection to a pressure transducer confirms venous cannulation.

The PAC may be associated with serious complications.[15] Arrhythmias, although frequent, usually resolve spontaneously.[83] However, between 1 and 3% require treatment.[15,153] Thrombosis and haemorrhagic lesions along the path of the PAC have been found in as many as 53% and 78% of patients, respectively, dying with a PAC *in situ*.[27]

Infections related to pulmonary artery catheterization are probably underestimated and have been thoroughly reviewed elsewhere.[112] Infections are more common with internal jugular placement, if catheters remain in place for longer than 4 days and if they are re-inserted at an old site.[25] Colonization of the catheter, usually by organisms from the skin of the insertion site, has been reported in approximately 22% of catheters on removal, the commonest organisms being *Staphylococcus epidermidis* and gram-negative bacilli. In approximately 1% of catheterizations, catheter colonizations may lead to bloodstream infection, commonly with *Staphylococcus epidermidis*, *Staphylococcus aureus* and yeasts. Septic thrombosis (infection of a thrombus which develops near the catheter) can cause a serious generalized infection despite the absence of local inflammatory signs.[91,112] Infective endocarditis exclusively caused by PAC occurs infrequently, although autopsy studies report an incidence of 2–7%.[112,142]

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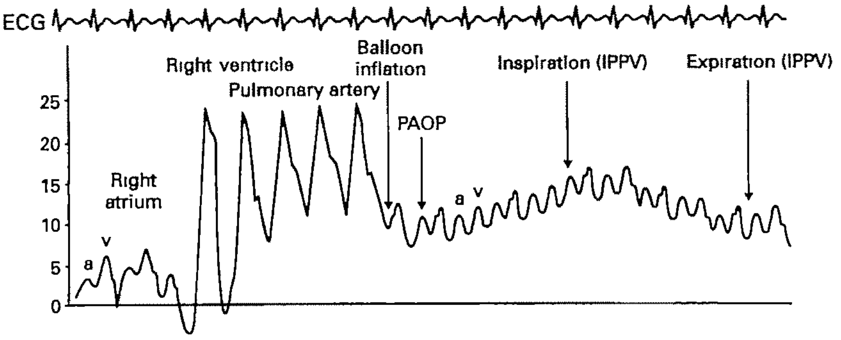

Figure 1 Representative traces during pulmonary artery catheterization and simultaneous real-time ECG recording. Note the occlusion "a" wave, the true PAOP, is in synchrony with the ECG "p" wave. Note also the pressure oscillations caused by a positive pressure respiratory cycle. IPPV=Intermittent positive pressure ventilation. Modified with permission from Wiedemann, Matthay and Matthay.[188]

Distal catheter migration occurs in up to 1% of insertions and may cause pulmonary infarction,[15] often presenting clinically as pulmonary embolism. Distal migration should be suspected if there is a continuous wedge trace with the balloon deflated or if minimal balloon inflation produces a wedge trace. A sudden increase in transduced pressure on balloon inflation suggests catheter abuttal against the pulmonary artery wall.

Pulmonary artery rupture is more common in patients more than 60 yr of age, those receiving anticoagulant therapy or those with pulmonary hypertension.[71] It is caused mostly by balloon overinflation.[71] Less frequently it can be caused by erosion of the balloon tip into the arterial wall.

Massive haemorrhage from pulmonary artery rupture has a reported incidence of 0.031–0.25% with a mortality of 25–83%.[15 93 153] Management by reversal of anticoagulation and high levels of PEEP has been successful occasionally,[151] but other therapies have often been used. These include selective endobronchial intubation with differential ventilation and transcatheter embolization.[51 146] Two reports suggest an apparent benefit from early surgical repair, which may require formal pulmonary resection.[93 177]

CONFIRMATION OF PLACEMENT

Correct placement of a PAC is accompanied by characteristic pressure wave changes leading to the atrial type waveform of pulmonary artery occlusion[188] (fig. 1). When properly wedged, the different pressures follow the relationship:

$$\text{PADP} > \text{PAOP}$$

where PADP and PAOP=pulmonary artery diastolic and occlusion pressure, respectively.

An important exception is severe mitral valve disease in which PAOP can be greater than PADP but remains less than MPAP.

Correct placement may also be confirmed by aspiration of "arterialized" blood from the catheter in the wedged position, as its oxygen tension (Pw_{O_2}) should be similar to Pa_{O_2}. However, if the catheter has floated into an area of low ventilation–perfusion match, this may not occur.[20]

Pressures in the pulmonary circulation

The physical characteristics required of systems designed to measure biological pressures have been reviewed extensively by Gardner and Hollingsworth.[59]

Inflation of the balloon isolates a pulmonary vascular segment, and flow in that segment ceases (fig. 2). As there are few precapillary anastomoses[38 75] the occluded segment is also isolated from flow in nearby non-occluded units. Therefore, downstream pressure in this occluded segment, pulmonary artery occlusion pressure (PAOP), equilibrates with pulmonary venous pressure (PVP). The balloon inflation technique does not measure the true pulmonary capillary pressure. In fact "pulmonary capillary wedge pressure" is a misleading hybrid term with no physiological correlate.[182 187] The pulmonary capillaries are not wedged and the pressure recorded when the pulmonary artery is occluded is not that of the capillaries.[184]

INTERPRETATION OF PAOP

At end-diastole, flow between the pulmonary valve and the mitral valve (which is still open) is minimal. End-diastole can be identified because the "a" wave on the wedge trace coincides with the "p" on the ECG (see fig. 1)[117]; sometimes one or both may be difficult to detect or non-existent, as in atrial fibrillation. Effectively there is a continuous column of

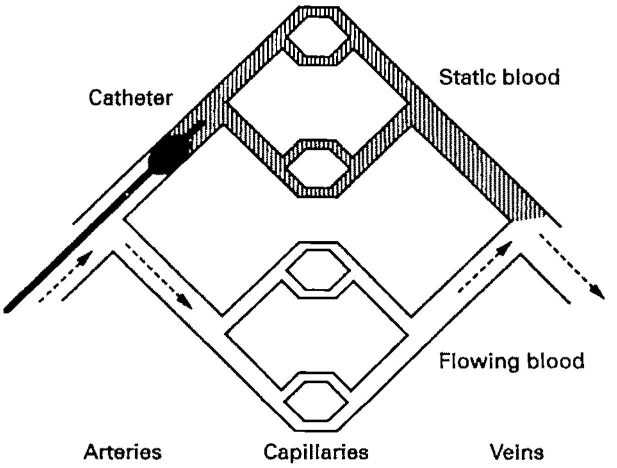

Figure 2 Diagrammatic representation of occlusion of a pulmonary arteriole by a balloon-tipped PAC. Note the absence of precapillary anastomoses, which explains why the pressure of the column of static blood (shaded area) equilibrates with downstream venous pressure. Modified from Weed[182] with permission.

Table 1 Discrepancies between PAOP and true preload (see text for detailed explanation)

Measurement discrepancy (boldface)	Reason	Comment
PAEDP>PAOP>PVP>LAP≈LVEDP α LVEDV	Tachycardia/increased PVR	End-diastolic pressure gradient PA → LA
PAEDP<"PAOP">PVP≈LAP≈LVEDP α LVEDV	West zones 1: $P_A>P_a>P_v$ West zones 2: $P_a>P_A>P_v$	catheter senses alveolar pressure, so true PAOP not measured
PAEDP≈PAOP≈PVP≈**LAP≠LVEDP** α LVEDV	Mitral stenosis, mitral regurgitation	**LAP>LVEDP; large 'a' wave** **LAP>LVEDP; large 'v' wave**
PAEDP≈PAOP≈PVP≈**LAP≠LVEDP** α LVEDV	Aortic regurgitation	**LAP<LVEDV**
PAEDP≈PAOP≈PVP≈**LAP≠LVEDP** α LVEDV	LV dysfunction	**LAP<LVEDP**
PAEDP≈PAOP≈PVP≈LAP≈**LVEDP ≠ LVEDV**	Low LV compliance High LV compliance	**LVEDP indicates a greater LVEDP** **LVEDP indicates a smaller LVEDV**

blood from the pulmonary artery to the left ventricle and all the pressures between these points (PAEDP, PVP, LAP and cavitary LVEDP) tend to equilibrate.[117, 122] Consequently, end-diastolic PAOP approximates LVEDP. In addition, it has been suggested that PAOP should be measured at end-expiration[122] when the effect of intrathoracic pressure is minimized. Discontinuation of IPPV to measure PAOP can introduce error caused by the variable relationship between PAOP and ventilation.[39]

The force of ventricular contraction is related to fibre length at end-diastole, which is determined by left ventricular end-diastolic volume (LVEDV).[124, 167] For a given ventricular compliance, LVEDP is directly proportional to LVEDV[188] so LVEDP and PAOP are indicative of left ventricular preload. It is crucial to understand that the PAC as an index of left ventricular preload depends on this LVEDP–LVEDV relationship remaining intact.

The assumption that PA occlusion always generates an uninterrupted column of blood is not always true and may lead to measurement errors. Table 1 summarizes the clinical circumstances, described below, in which PAEDP, PAOP and LVEDP cannot be assumed to be equal.

PAEDP different from LVEDP

Occasionally when it is difficult to obtain PA occlusion pressure, pulmonary artery diastolic pressure is used instead. When diastole is short (heart rate >115 beat min^{-1}) or there is impairment to flow, such as in pulmonary hypertension, flow may not cease and pressures between the pulmonary artery and left atrium do not equilibrate. Consequently, PAEDP remains greater than LAP[14, 87] with PAOP somewhere between the two.[100]

PAOP different from PVP

When the catheter tip is in a West zone 1 or 2,[186] high alveolar pressure may interrupt the channel of blood between the pulmonary artery and left atrium.[188] In these situations the catheter sensor reflects alveolar and not vascular pressure. The erroneous "PAOP" is higher than PADP or may have a marked inspiratory swing.[122] In patients with high airway pressures or hypovolaemia, or both, West zones 1 and 2 occupy a proportionately greater volume of lung.[154] In these situations the PAC is more likely, relative to normal conditions, to float into zones 1 and 2 or to become lodged in areas which convert to zones 1 and 2, for example after patient positioning.

The effect of PEEP on PAOP depends on compliance of the lung.[22] Compliant lungs transmit a greater proportion of the applied pressure to the microvasculature than non-compliant lungs. As an approximation, PAOP should increase by no more than half of the PEEP increment.[117, 122] Greater increases suggest catheter tip placement in West zone 1 or 2.

LAP different from LVEDP

In mitral valve disease the increase in left atrial pressure (LAP), reflected in PAOP, overestimates LVEDP. In mitral stenosis the PAOP trace has a characteristic large "a" wave. In mitral regurgitation the "v" wave is large. Other causes of large v wave include any mechanism that increases pulmonary venous flow such as left to right shunt.[117, 122]

Conversely, in left ventricular dysfunction, LAP underestimates LVEDP because left atrial ejection into a stiff ventricle causes a greater increase in the latter's pressure.[14, 49, 133] In aortic regurgitation LAP is also less than LVEDP.[76]

Altered LVEDP/LVEDV relationship (left ventricular compliance)

Myocardial ischaemia, pericardial disease, aortic stenosis, shock and other causes of increased left ventricular stiffness lead to a greater LVEDP for a given ventricular filling volume.[54, 58] The reduction in compliance is reflected in an increased PAOP which overestimates true preload.

Conversely, dilated cardiomyopathies are associated with increased ventricular compliance and PAOP may underestimate ventricular filling.[117] Ventricular compliance also varies in response to afterload changes and inotropes.[1]

PULMONARY CAPILLARY PRESSURE

Pulmonary capillary pressure (P_c) is an important determinant of transvascular filtration.[38, 167] Although P_c can be measured by direct micropuncture[8] or by the isogravimetric technique in isolated perfused lungs[57] there is no practical method *in vivo*.

In health, P_c is usually 5–10 mm Hg and can be estimated from PAOP using the following relationship:

$$P_c = \text{PAOP} + 0.4\,(\text{MPAP} - \text{PAOP}).$$ [57, 79]

The value 0.4 was obtained from dog experiments in which the resistance from pulmonary capillary to vein accounted for 44% of the total pulmonary vascular resistance whereas the resistance between

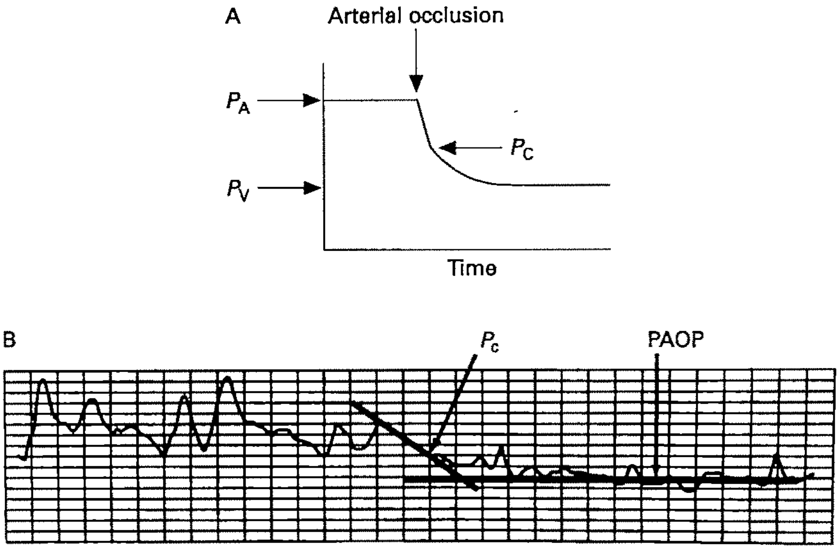

Figure 3 Estimation of pulmonary capillary pressure (P_c) from inspection of the pulmonary artery pressure (PAP) trace immediately after balloon occlusion. A: Theoretical pressure decay curve, with P_c marking the inflection point between the two limbs of the curve; reproduced with permission from Holloway and colleagues.[79] B: Actual bi-exponential pressure drop. Note P_c is significantly greater than PAOP but not "halfway" between mean PAP and PAOP, illustrating the uneven distribution of pulmonary vascular resistance. Reproduced from Levy[102] with permission.

pulmonary artery and capillary accounted for 56% of the total PVR. This is why P_c is normally closer to PAOP than to MPAP.[32]

However, patients with sepsis or acute lung injury may have a normal PAOP but high P_c with the linear relationship between the two being lost.[31,32] In these conditions, pulmonary oedema, which is traditionally attributed to abnormal capillary permeability, may have an important hydrostatic component, shown by an increased P_c. This implies that therapy monitored by PAOP may not always be successful.

In these circumstances it might be useful to estimate P_c by analysis of the curve resulting from pulmonary artery balloon occlusion (fig. 3) which shows biexponential decay. The initial rapid pressure decrease towards P_c is caused by the sudden absence of upstream pressure. The slower pressure decrease from P_c towards PVP is the result of the discharge of blood from the capillary capacitance vessels into the pulmonary venules. The inflection point is taken to be P_c.[79]

This estimated P_c has been validated against a wide range of predicted PCP values based on the isogravimetric technique.[57] The latter has itself been validated against direct occlusion measurements in isolated lungs[173] and is known to correlate well with direct micropuncture measurements.[8,32]

Further, for a given patient, the position of this inflection point (P_c) on the decay curve illustrates the relationship between pulmonary arterial and venous resistances and helps determine the location of the increased PVR. The higher the P_c on the curve, the less arterial resistance contributes to PVR. Recent studies suggest that alveolar hypoxia tends to increase pulmonary vascular resistance predominantly upstream of the capillaries (Ra), whereas sepsis, pulmonary hypertension[143] and acute lung injury usually cause an increase in pulmonary resistance downstream of the capillaries (Rv).[30,160,187]

However, there is concern that these small nuances can be overwhelmed by the magnitude of errors in measuring PAOP.[63] These and other issues in pulmonary capillary pressure are reviewed elsewhere.[30,102]

Thermodilution cardiac output

Measurement of cardiac output using the PAC is based on injection of a tracer into the right atrium and analysis of the change of its concentration over time in the pulmonary artery.[70,168] It is assumed that the mass (M) of the substance injected remains constant and therefore equals the product of the mean tracer concentration (measured in the PA) and its volume of distribution. It can be shown that M is equal to the product of flow and the integral of concentration over time,[18,50,183] expressed by the equation:

$$M=\dot{Q}\times\int C(t)\,dt$$

where $\dot{Q}$=flow and represents right ventricular cardiac output.

Currently the preferred method is to inject a cold solution and then monitor pulmonary artery blood temperature. The equation above can be expressed with reference to temperature as:

$$V_i\,(T_b-T_i)\,K_1\,K_2=\dot{Q}\times\int \text{Temp}\,dt$$

and

$$\dot{Q}=V_i\,(T_b-T_i)\,K_1\,K_2/\int \text{Temp}\,dt$$

where V_i and T_i=volume and temperature of injectate, respectively, T_b=blood temperature, Temp= difference between the initial temperature and the new temperature in the pulmonary artery; K_1 unifies units and relates the specific heat and gravity of injectate to blood and K_2 relates the injectate and deadspace volumes.

Despite empirical correction factors and rapid injection of tracer fluid, heat transfer to right atrial blood, catheter wall and surrounding tissues may lead to overestimation of cardiac output.[18,86,185] Baseline fluctuations in pulmonary artery temperature,[125,183] abnormal haematocrit values and intracardiac shunts are other potential sources of error.[121]

For convenience there has been a trend to use room temperature injectate in everyday practice. The signal-to-noise ratio obtained with 10 ml of injectate at room temperature is adequate for most circumstances with cardiac indices of 2.6–4.2 litre min^{-1} m^{-2}.[98,137,179]

The effect of IPPV on cardiac output measurement throughout the respiratory cycle is complex. Predictably, during IPPV cardiac output measurements are highest at end-expiration. Positive end expiratory pressure (PEEP) decreases preload and mean cardiac output, particularly in hypovolaemic patients[86,109,180] although some have found that the response to PEEP, particularly in ischaemic heart disease, is more heterogenous.[148]

For these reasons variations of up to 25% can occur between single measurements and it is customary to average three measurements taken randomly throughout the respiratory cycle[2] and to be guided by trends rather than absolute values.

Continuous cardiac output and mixed venous oxygen saturation

More recent PAC developments have enabled near continuous thermodilution calculation of cardiac output (CCO).[189] A heating filament is attached to a pulmonary artery catheter such that it comes to lie in the right ventricle. Pulses of heat produced by the filament are detected by the thermistor sited in the distal tip of the PAC. Changes in distal pulmonary artery temperature produce a thermodilution-like washout. Measurements are updated every 30 s and averaged over several minutes.

CCO appears as accurate and reproducible as intermittent thermodilution calculations over a large number of diverse patients.[21,113] Although it is clearly not truly continuous CCO is potentially better than intermittent measurements, typically several hours apart.[119]

CCO has the advantage of eliminating the potential errors associated with variations in volume and speed of tracer injection. Nevertheless, rapid fluid infusions may change PA blood temperature and affect its accuracy.[45,119]

Pulmonary artery catheters capable of measuring continuous $S\bar{v}_{O_2}$ by fibreoptic oximetry have been available since the early 1970s.[110,119] Based on the Fick principle it follows that cardiac output, oxygen consumption and arteriovenous oxygen difference are related such that when oxygen consumption is constant, changes in mixed venous oxygen content (and $S\bar{v}_{O_2}$) are directly proportional to cardiac output.[89,181]

Normally there is good correlation between cardiac output and $S\bar{v}_{O_2}$, although if oxygen consumption fluctuates a decrease in $S\bar{v}_{O_2}$ may be caused by a decrease in cardiac output or by an increase in oxygen extraction.[120] Nevertheless, $S\bar{v}_{O_2}$ reflects the overall balance between oxygen supply and consumption.[119] Other potential problems include measurement errors caused by methaemoglobinaemia, carboxyhaemoglobinaemia and non-linearity of the haemoglobin oxygen dissociation curve.[4,110]

Some of the interpretation difficulties outlined above may be overcome when simultaneous $S\bar{v}_{O_2}$, arterial saturation and cardiac output readings are combined. If cardiac output is unchanged, arterial desaturation with a widening gap between Sa_{O_2} and $S\bar{v}_{O_2}$ suggests an increased extraction ratio (fig. 4A). If Sa_{O_2} remains relatively unchanged, a decrease in $S\bar{v}_{O_2}$ normally represents an increase in oxygen extraction to compensate for the reduced oxygen delivery associated with a low cardiac output (fig. 4B).

Right ventricular ejection fraction (RVEF)

RVEF can be determined from the thermodilution curve by analysis of successive diastolic plateaus using a PAC equipped with a rapid response thermistor.[92] More recently, techniques based on computer algorithms[43] and systolic time intervals[67] have been introduced.

In order to avoid inaccuracies in estimating RVEF it is important to position the PAC carefully. Ideally, the injection port should be in the right atrium as near as possible to the tricuspid valve; the thermistor should be in the pulmonary artery just distal to the pulmonary valve.[165] When heart rate is erratic or very fast, RVEF is technically difficult to obtain. Also, RVEF is too dependent on right ventricular afterload to be a good indicator of right ventricular contractility.[120] However, it can be used to calculate right ventricular end-diastolic volume (RVEDV) and other right ventricular derived variables from the formula: RVEDV=SV/RVEF.

It has been suggested that RVEDV is a more accurate indicator of preload and correlates better with cardiac output and right and left ventricular work indices than RAP or PAOP.[44,138,148] This is understandable when one considers the complex interactions between positive pressure ventilation, PEEP, vasoactive agents, ventricular compliance and venous tone,

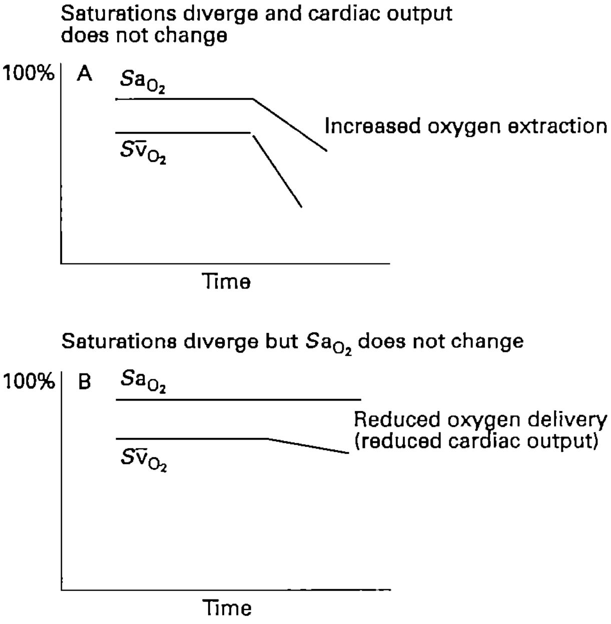

Figure 4 Simultaneous recordings of mixed venous ($S\bar{v}_{O_2}$) and arterial (Sa_{O_2}) saturations in two common situations of changing tissue oxigenation. A: Cardiac output is unchanged and tissue oxygenation worsens because of increased oxygen extraction B: Arterial oxygenation remains constant, but a decrease in cardiac output causes a decrease in oxygen delivery.

all of which can increase PAOP while decreasing actual ventricular volume. However, as the net effect of such factors on overall cardiac output can be monitored directly, it can be argued that calculation of RVEDV, despite being more accurate, contributes little additional information. Further, the mathematical relationship between RVEDV and SV increases the possibility of artefactual coupling as a possible cause of the correlation between the two.[120]

The case for measurement of RVEDV is stronger in sepsis,[95 135] pulmonary hypertension[144 191] and ARDS[159 163] where right ventricular function is a major determinant of cardiac output.[128] In addition, high PEEP levels are normally necessary in the management of these conditions and this makes preload assessment by pressure (PAOP) measurements less reliable.[120]

Pulmonary artery catheterization in practice

Between 1989 and 1994, a prospective observational study was conducted involving 5735 patients treated in 15 intensive care units in five teaching centres in the US.[28] This work was an extension of previous studies restricted to patients with myocardial infarction[66 192] because it included, in addition, patients with congestive heart failure, chronic obstructive pulmonary disease, acute respiratory failure, sepsis, multi-organ failure and four other disease categories. Treatment selection bias was adjusted by case matching, multivariate analysis and a propensity score, itself a source of controversy.[136 176]

It reported a significantly increased risk of death at 30 days in patients managed with a PAC, as follows: odds ratio (OR) of 1.24 in 1008 pairs of patients case matched to adjust for treatment bias, and OR of 1.21 in the total patient group of 5735 after multivariate analysis to adjust for treatment bias. In addition, the PAC group had longer length of stay in the ICU and increased direct hospital costs.[28]

The result of the study by Connors and colleagues[28] raised concern that pulmonary artery catheterization might be partly responsible for an increased mortality, either directly or by leading to potentially harmful treatment.[37 164] A recent task force analysed the evidence from clinical studies involving PAC-guided management in a variety of clinical groups.[129] In many patient groups the evidence was either weak or inconclusive.

Given such controversy, the impact of the PAC on patient outcome might be judged from clinical studies of PAC derived management changes. However, few such studies, mostly limited to perioperative care, include patients managed without PAC-derived information.[5 68 85 175] This is largely because of the ethics of depriving patients of an instrument previously considered as beneficial. The setting appears to be set for large randomized, controlled studies on the issue of PAC-guided management[29 37 129 136] or, at the very least, a re-evaluation of its use.[164 176]

In critical care and anaesthesia there have been principally three indications for pulmonary artery catheterization: diagnosis, guidance of fluid and vasoactive drug administration, and close observation of cardiopulmonary interactions. In practice this includes four areas which are discussed below.

ASSESSMENT OF INTRAVASCULAR VOLUME, ADEQUACY OF CARDIAC OUTPUT AND OXYGEN TRANSPORT

For many years right heart catheterization with the PAC has been standard in assessing left ventricular preload and therefore intravascular volume status.[53] However, PAOP does not always correlate with left ventricular preload, particularly in non-compliant hearts,[58] left ventricular dysfunction,[14 49] myocardial ischaemia,[54 133] valvular heart disease or patients receiving vasoactive therapy,[1] all traditional indications for insertion of a PAC. Nevertheless, subsequent studies revealed inaccurate "bedside" estimation of haemodynamic variables compared with PAC readings.[26 47] This is perhaps inevitable if the PAC is used as the gold standard; the reverse would likely be true were clinical signs taken as the gold standard. These observed inaccuracies were used to support PAC catheterization. But there seems to be poor understanding and incorrect interpretation of PAC-derived data.[64 82]

But even when the PAC data are interpreted correctly and indicate true preload, we do not know if given values are adequate or what is the individual optimum preload. For example, most clinicians would find that a cardiac index of 3 litre min^{-1} m^{-2} is more than expected, immediately after heart surgery, too little for a 20-yr-old trauma victim and possibly adequate for an 80-yr-old with sepsis. Other technologies[104 105 161] are becoming popular but again do not indicate if the cardiac output achieved is effective.

The PAC is also used to calculate systemic and pulmonary haemodynamic data (table 2) and oxygen transport values (table 3). The physiological response to trauma, anaesthesia and major surgery has long been the subject of interest.[24 33 40 152 155 171] Oxygen transport studies in high-risk surgical patients found higher levels of cardiac index (CI), oxygen delivery index [$\dot{D}o_2I$] and oxygen consumption index ($\dot{V}_{o_2}I$) among survivors than in non-survivors. Low oxygen transport indices were proposed as a cause of tissue hypoxia and death.

Shoemaker and colleagues suggested that the median values among survivors be used as therapeutic goals.[11 158] Numerous studies used the PAC to guide augmentation of oxygen transport, with the aim of treating underlying tissue hypoxia.

In prospective studies to test this hypothesis patients treated to achieve target values in CI, [$\dot{D}o_2I$] and $\dot{V}_{o_2}$ had much higher survival rates.[156 157] This was further supported in patients undergoing peripheral limb surgery[5] and in a prospective randomized study of high-risk surgical patients.[16] In septic shock, similar therapy was also associated with improved outcome compared with historical controls[46] or with subgroups created retrospectively.[174 190]

However, these encouraging results were not replicated when predominantly septic patients were randomized after entry to an ICU. Hayes and colleagues found that patients receiving aggressive management with fluids and, when necessary, inotropes to achieve target haemodynamic goals had higher mortality than controls treated to reach acceptable baseline haemodynamic values.[72] Further, in a much larger study, when supranormal cardiac output was the sole goal, patients did no better than those who remained

Table 2 Measured haemodynamic variables

Variable	Normal range (units)
Central venous pressure (CVP)	0–8 mm Hg
Right ventricular systolic pressure (RVSP)	15–30 mm Hg
Right ventricular end-diastolic pressure (RVEDP)	0–8 mm Hg
Pulmonary artery (systolic) pressure (PAP)	15–30 mm Hg
Pulmonary artery diastolic pressure (PADP)	4–12 mm Hg
Pulmonary artery occlusion pressure (PAOP)	2–12 mm Hg
Cardiac output ($\dot{Q}$)	Varies with size, age and sex
Mixed venous oxygen saturation ($S\bar{v}_{O_2}$)	75%

as controls or who were treated to achieve a "normal" $S\bar{v}_{O_2}$.[60]

Unfortunately, even the most rigorous studies have neither separated supportive from definitive treatment (correct antibiotics, timely surgery, etc.) nor established that the latter was balanced between study groups. Overall, those patients with sufficient cardiorespiratory reserve to increase their oxygen delivery[16 174] and utilization[73 74] appear to have a better chance of survival. Those with less cardiorespiratory reserve treated to achieve supranormal targets have, at best, no better outcome than similar patients managed within their physiological limitations.[77] There is no convincing evidence that attemping to increase cardiac index indiscriminantly across a wide cross section of critically ill patients improves outcome[60 72] and some evidence indicates it may increase mortality.[72]

The emphasis in cardiovascular resuscitation has shifted away from "routinely" attempting to obtain goals for which the PAC is a prerequisite, to management adjusted to individual cardiac performance. This might be acomplished by determining if cardiac output is effective, initially predominantly by clinical assessment, and later complemented by pulmonary artery catheterization. An effective cardiac output (ECO) could be defined as that which achieves normal premorbid arterial pressure with warm peripheries at a heart rate of less than 100 beat min^{-1}, irrespective of supportive therapy. The effectiveness of peripheral perfusion can later be assessed by biochemical analyses such as acid–base balance, gastric intra-mucosal acid estimation and blood lactate concentration. However, it is important to consider that these biochemical markers can be deranged for reasons other than haemodynamics (i.e. hepatic or renal failure, or both).

MYOCARDIAL DYSFUNCTION

Patients with acute MI complicated by congestive cardiac failure or hypotension in whom treatment was guided by a PAC had a higher mortality rate than those managed without it, even after multivariate analysis to adjust for disease severity.[66 192] These studies were retrospective and were unable to exclude that sicker patients received PAC, but the direct mortality associated with PAC was a possibility. As a result, reassessment of the PAC was advocated.[36 139]

When the PAC has been used to guide management in elective coronary artery bypass grafting[175] and abdominal aneurysm surgery[85] there has also been no difference in serious end-organ complications or mortality. Furthermore, placement of a PAC electively or after haemodynamic deterioration did not appear to affect outcome, suggesting that conventional indicators of the need for PAC may be unreliable.[175]

Perioperative myocardial ischaemia is an important cause of postoperative cardiac morbidity and mortality.[107 108] Despite conflicting accounts of the role of the PAC in the detection of myocardial ischaemia[69 85 178] it is useful in detecting haemodynamic events, such as decrease in cardiac output, stroke work or mixed venous oxygenation or an increase in PAOP, which normally are associated with myocardial ischaemia. Earlier work indicated that when used as part of a management strategy designed to avoid adverse haemodynamic fluctuations, the PAC helped to reduce perioperative cardiac events.[134] There is, however, no definitive evidence favouring the use of PAC in patients at risk of perioperative cardiac dysfunction undergoing major surgery.[129]

Table 3 Derived haemodynamic variables. DAP=Diastolic arterial pressure; SAP=systolic arterial pressure; Hb=haemoglobin; $P\bar{v}_{O_2}$=mixed venous oxygen tension

Variable	Calculation	Normal range
Body surface area (BSA)	Weight $(kg)^{0.425}$×height $(cm)^{0.725}$×0.007184	
Mean arterial pressure (MAP)	DAP + 1/3×(SAP–DAP)	70–105 mm Hg
Cardiac index (CI)	$\dot{Q}$/BSA	2.8–4.2 litre min^{-1} m^{-2}
Stroke volume (SV)	Q/HR	80 ml
Stroke index (SI)	SV/BSA	30–65 ml m^{-2}
Left ventricular stroke work index (LVSWI)	CI×(MAP–PAOP)×0.0136	44–64 g m^{-1} m^{-2}
Systemic vascular resistance (SVR)	(MAP–CVP)×80/Q	1000–1200 dyn s cm^{-5} m^{-2}
Systemic vascular resistance index (SVRI)	(MAP–CVP)×80/CI; (nb SVRI=SVR×BSA)	1600–2400 dyn s cm^{-5} m^{-2}
Mean pulmonary artery pressure (MPAP)	MPAP+1/3×(PAP–PADP)	9–16 mm Hg
Right ventricular stroke work index (RVSWI)	CI×(MPAP–CVP)×0.0136	7–12 g m^{-1} m^{-2}
Pulmonary vascular resistance (PVR)	(MPAP–PAOP)×80/Q	60–120 dyn s cm^{-5} m^{-2}
Pulmonary vascular resistance index (PVRI)	(MPAP–PAOP)×80/CI; (nb PVRI=PVR×BSA)	250–340 dyn s cm^{-5} m^{-2}
Arterial oxygen content (Ca_{O_2})	Sa_{O_2}×Hb×1.39+Pa_{O_2} (mm Hg)×0.003	180 ml $litre^{-1}$
Mixed venous oxygen content ($C\bar{v}_{O_2}$)	$S\bar{v}_{O_2}$×Hb×1.39+Pv_{O_2} (mm Hg)×0.003	130 ml $litre^{-1}$
Oxygen delivery (Do_2)	Q×Ca_{O_2}	850–1050 ml min^{-1}
Oxygen consumption ($\dot{V}o_2$)	$\dot{Q}$×(Ca_{O_2}–Cv_{O_2})	180–300 ml min^{-1}
Oxygen delivery index (Do_2I)	Do_2/BSA	520–650 ml min^{-1} m^{-2}
Oxygen consumption index (Vo_2I)	Vo_2/BSA	110–180 ml min^{-1} m^{-2}

ACUTE LUNG INJURY

Acute lung injury (ALI) and its most severe form ARDS[3] are characterized by refractory hypoxaemia, widespread alveolar infiltrates on chest x-ray and respiratory distress not caused by but which may coexist with increased left atrial pressure.[7] The destruction of the alveolo-capillary membrane, inflammatory alveolar exudate[10] and subsequent fibrotic response[35] lead to alveolar oedema, reduced lung compliance, increased venous admixture and hypoxaemia.[96] Pulmonary vasoconstriction can worsen ventilation–perfusion mismatch and cause pulmonary hypertension with increased right ventricular work.[191]

In ALI high capillary permeability and increased capillary pressures coexist.[30,166] There is currently no treatment that can reverse the former.[149] Therefore, it might be more important to reduce pulmonary capillary hydrostatic pressure, in an attempt to minimize alveolar oedema,[111,149] and to decrease pulmonary vascular resistance in order to reduce pulmonary hypertension.

There is no conclusive evidence that pulmonary artery catheterization affects outcome in ARDS. However, especially when high levels of PEEP are used, it might be justifiable to use PAC in the diagnosis of ARDS and to measure the variables to be manipulated; these include PAOP and the pulmonary vascular and right ventricular haemodynamic indices.

Reduction of alveolar oedema

As the early manifestations of ARDS include alveolar and interstitial fluid accumulation, therapy leading to removal of alveolar fluid may improve gas exchange. Indeed numerous studies suggest that fluid restriction may be beneficial.[150] In retrospective analyses a favourable fluid balance[147] and a reduction in PAOP[80] were associated with less ventilator, ICU and hospital days. When the guide to fluid reduction was extravascular lung water (EVLW) (measured by double indicator dilution[103,162]), there was a reduction in ICU and hospital stay[114] and, after retrospective subdivisions, mortality.[48] However, these studies may be taken as markers of less severe illness, in as much as they reflect ability to withstand fluid elimination without detriment.

Nevertheless, there is widespread agreement that in some patients excessive fluid reduction may worsen cardiovascular performance and compromise organ perfusion.[81,150,172] In practice the ability to remove enough fluid to improve oxygenation depends on whether this can be done without life threatening hypoperfusion, particularly if the underlying sepsis remains uncontrolled. Furthermore, as the relationship between PAOP, P_c, alveolar fluid and oxygenation is complex[30,79,102,160] the impact of lowering PAOP on alveolar fluid is unpredictable. On balance it seems appropriate to reduce PAOP in the early exudative phase of ARDS cautiously to a level which does not compromise cardiovascular function or organ perfusion. The possible benefit of cautious fluid restriction and diuresis for more than 3 or 4 days remains to be determined.[96]

Selective pulmonary vasodilatation

Patients with severe ARDS and acute lung injury may develop pulmonary hypertension (PHT) with significant right ventricular dysfunction[159,191] and loss of hypoxic pulmonary vasoconstriction.[19] Traditional i.v. vasodilators used to control pulmonary hypertension can lead to worsening intrapulmonary shunt, systemic hypotension and impaired oxygenation.

In the past few years inhaled nitric oxide has been used as an alternative pulmonary vasodilator. Nitric oxide is an endogenous gas[84,123] with potent vascular smooth muscle relaxant properties.[115] It preferentially vasodilates ventilated lung segments[56,61,127] and can improve ventilation–perfusion matching and reduce pulmonary arterial pressure with little systemic hypotension.[9,13,126,130,132,141] Nitric oxide also reduces right ventricular afterload[52] and pulmonary hypertension attributable in part to permissive hypercapnia.[131]

The results of the first randomized, controlled phase II trial of placebo *vs* nitric oxide at various doses have become available.[41] Although nitric oxide was well tolerated, it did not improve mortality. However, a relatively large proportion (60%) of patients receiving nitric oxide responded with an increase in oxygenation in the first 4 h, but this was small and not long lasting. There was a decrease in mean PAP which was also small (approximately 2 mm Hg) and short-lived.

PULMONARY HYPERTENSION

PHT caused by chronic obstructive lung disease,[106,145] left heart disease and thromboembolic disease[116] is commonly encountered in the intensive care patient. Many general treatments of these conditions and more specific treatments of PHT (discussed above) affect right and left heart performance. Therefore, the PAC becomes useful to monitor pulmonary artery pressure, and ventricular and systemic haemodynamic responses to therapy.

Conclusion

Pulmonary artery catheterization is over half a century old. It is a valuable educational tool and facilitates quantification of the clinical assessment of cardiorespiratory performance. However, the PAC has also taken the clinician away from patients and encouraged decisions based on numerical targets, thus detracting from the concept of individualized supportive therapy.

The PAC still has a significant role in patient management, primarily as a method for diagnosis and monitoring haemodynamic responses to therapy. In common with every other instrument, it has drawbacks. Its insertion delays immediate therapy, introduces infection and may precipitate iatrogenic events. If it allows us to adjust clinical assessment and supportive therapy it will have achieved its goal. On the other hand, if it promotes hands off haemodynamic management it will be criticized unfairly and may be superseded by other technologies which could go through the same cycle.

References

1. Alderman EL, Glanz SA. Acute hemodynamic interventions shift the diastolic pressure–volume curve in man. *Circulation* 1976; **54**: 6262–6271.
2. Armengol J, Man GCW, Balsys AJ, Wells AL. Effects of the respiratory cycle on cardiac output measurements: reproducibility of data enhanced by timing the thermodilution injections in dogs. *Critical Care Medicine* 1981; **9**: 852–854.
3. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319–323.
4. Bennett D, Boldt J, Brochard L, Coriat P, Dhainaut JF, Edwards D, Feihl F, Groeneveld J, Lamy M, Lundberg D, Lemaire F, Payen D, Perret C, Reiz S, Rouby JJ, Scheidegger D, Singer M, Suter P, Thijs L, Vincent JL. Expert Panel: The use of the pulmonary artery catheter. *Intensive Care Medicine* 1991, **17**: I–VIII.
5. Berlauk JF, Abrams JH, Gilmour IJ, O'Connor SR, Knighton DR, Cerra FB. Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery. *Annals of Surgery* 1991; **214**: 289–299
6. Bernard C. *Leçons sur la Chaleur Animale*. Paris: Librairie JB Balliere et Fils, 1876.
7. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American–European Consensus Conference on ARDS Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: 818–824.
8. Bhattacharya J, Staub NC. Direct measurements of microvascular pressures in the isolated perfused dog lung. *Science* 1980; **210**: 327–328.
9. Bigatello LM, Hurford WE, Kacmarek RM, Roberts JDJ, Zapol WM. Prolonged inhalation of low concentrations of nitric oxide in patients with severe adult respiratory distress syndrome. Effects on pulmonary hemodynamics and oxygenation. *Anesthesiology* 1994; **80**: 761–770.
10. Bigatello LM, Zapol WM. New appproaches to acute lung injury. *British Journal of Anaesthesia* 1996; **77**: 99–109.
11. Bland RD, Shoemaker WC, Abraham E, Cobo JC. Hemodynamic and oxygen transport patterns in surviving and nonsurviving postoperative patients. *Critical Care Medicine* 1985; **13**: 85–90.
12. Bone RC. High tech predicament: pulmonary artery catheter. *Journal of the American Medical Association* 1990; **264**: 2933
13. Bone RC. A new therapy for the adult respiratory distress syndrome. *New England Journal of Medicine* 1993; **328**: 431–432.
14. Bouchard RJ, Gault JH, Ross J. Evaluation of pulmonary arterial end-diastolic pressure as an estimate of left ventricular end-diastolic pressure in patients with normal and abnormal left ventricular performance. *Circulation* 1971; **44**: 1072–1079.
15. Boyd KD, Thomas SJ, Gold J, Boyd AD. A prospective study of complications of pulmonary artery catheterizations in 500 consecutive patients. *Chest* 1983; **84**: 245–249.
16. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high risk surgical patients. *Journal of the American Medical Association* 1993; **270**: 2699–2707
17. Bradley RD. Diagnostic right heart catheterisation with miniature catheters in severely ill patients. *Lancet* 1964; **2**: 941–942.
18. Branthwaite MA, Bradley RD. Measurement of cardiac output by thermodilution in man. *Journal of Applied Physiology* 1968; **24**: 434–438.
19. Brett SJ, Evans TW. Inhaled vasodilator therapy in acute lung injury: first, do NO harm? *Thorax* 1995; **50**: 821–823.
20. Brewster H, McIlroy MB. Blood gas tensions and pH of pulmonary "wedge" samples in patients with heart disease. *Journal of Applied Physiology* 1973; **34**: 413–416.
21. Burchell SA, Yu M, Takiguchi SA, Ohta RM, Myers SA. Evaluation of a continuous cardiac output and mixed venous oxygen saturation catheter in critically ill surgical patients. *Critical Care Medicine* 1997; **25**: 383–391.
22. Chapin JC, Downs JB, Douglas ME, Murphy EJ, Ruiz B. Lung expansion, airway pressure transmission and positive end-expiratory pressure. *Archives of Surgery* 1979; **114**: 1193–1197.
23. Chauveau A, Marey EJS. *Physiologie medicale de la circulation du sang*. Paris: Delahaye, 1863.
24. Clowes G, Vucinic M, Weidner MG. Circulatory and metabolic alterations associated with survival or death in peritonitis. *Annals of Surgery* 1966; **163**: 866–885.
25. Cobb DK, High KP, Sawyer RG, Sable CA, Adams RB, Lindley DA, Pruett TL, Schwenzer KJ, Farr BM. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *New England Journal of Medicine* 1992; **327**: 1062–1068.
26. Connors A, McCaffree D, Gray BA. Evaluation of right-heart catheterization in the critically ill patient without acute myocardial infarction. *New England Journal of Medicine* 1983; **308**: 263–267.
27. Connors AF jr, Castele RJ, Farhat NZ, Tomashefski JF jr. Complications of right heart catheterization. A prospective autopsy study. *Chest* 1985; **88**: 567–572.
28. Connors AFJ, Speroff T, Dawson NV, Thomas C, Harrell FEJ, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJJ, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA. The effectiveness of right heart catheterization in the initial care of critically ill patients. *Journal of the American Medical Association* 1996; **276**: 889–897.
29. Cooper AB, Doig GS, Sibbald WJ. Pulmonary artery catheters in the critically ill. An overview using the methodology of evidence-based medicine. *Critical Care Clinics* 1996; **12**: 777–794.
30. Cope DK, Grimbert F, Downey JM, Taylor AE Pulmonary capillary pressure: a review. *Critical Care Medicine* 1992; **20**: 1043–1056.
31. Cope DK, Parker J, Taylor MD, Houston M, Taylor AE. Pulmonary capillary pressures during hypoxia and hypoxemia. Experimental and clinical studies. *Critical Care Medicine* 1989; **17**: 853–857.
32. Cope DK, Taylor AE. Clinical use of pulmonary capillary pressure: a technique whose time has arrived. *Critical Care Medicine* 1993; **21**: 808–810.
33. Cournand A. Studies of the circulation in clinical shock. *Surgery* 1943; **13**: 964–965.
34. Cournand A, Lauson HD, Bloomfield RA, Breed ES, Baldwin E de F. Recording of right heart pressures in man. *Proceedings of the Society for Experimental Biology and Medicine* 1944; **55**: 34–36.
35. Crouch E. Pathobiology of pulmonary fibrosis. *American Journal of Physiology* 1990; **3** L159–L184.
36. Dalen JE. Does pulmonary artery catheterization benefit patients with acute myocardial infarction? *Chest* 1990; **98**: 1313–1314.
37. Dalen JE, Bone RC. Is it time to pull the pulmonary artery catheter? *Journal of the American Medical Association* 1996; **276**: 916–918.
38. Dawson CA, Linehan JH, Rickaby DA. Pulmonary microcirculatory hemodynamics. *Annals of the New York Academy of Sciences* 1982; **384**: 90–106.
39. DeCampo T, Civetta JM. The effect of short-term discontinuation of high level PEEP in patients with acute respiratory failure. *Critical Care Medicine* 1979; **7**: 47–49.
40. Del Guercio LRM. Pulmonary arteriovenous admixture and the hyperdynamic state in surgery for portal hypertension. *Surgery* 1964; **56**: 57–74.
41. Dellinger R, Zimmerman J, Taylor R, Straube R, Hauser D, Criner G, Davis KJ, Hyers T, Papadakos P, Group at INOiAS Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. *Critical Care Medicine* 1998; **25**: 15–23.
42. Dexter L, Haynes FW, Burwell CS, Eppinger EC, Sagerson RP, Evans JM. Studies of congenital heart disease, II: The pressure and oxygen content of blood in the right auricle, right ventricle, and pulmonary artery in control patients, with observations on the oxygen saturation and sources of pulmonary 'capillary' blood. *Journal of Clinical Investigations* 1947; **26**: 554–560.
43. Dhainaut JF, Brunet F, Monsallier F, Villemant D, Devaux JY, Konno M, De Gournay JM, Armaganidis A, Iotti G, Huyghebaert MF Bedside evaluation of right ventricular performance using a rapid computerized thermodilution method. *Critical Care Medicine* 1987; **15**. 148–152.
44. Diebel LN, Wilson RF, Tagett MG, Kline RA. End-diastolic volume. A better indicator of preload in the critically ill. *Archives of Surgery* 1992; **127**: 817–821
45. Edwards JD. Continuous thermodilution cardiac output: A significant step forward in hemodynamic monitoring. *Critical Care Medicine* 1997; **25**: 381–382
46. Edwards JD, Brown CS, Nightingale P, Slater RM, Faragher EB. Use of survivors' cardiorespiratory values as therapeutic goals in septic shock. *Critical Care Medicine* 1989; **17**: 1098–1103.

47. Eisenberg P, Jaffe A, Schuster D. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. *Critical Care Medicine* 1984; **12**: 549–553.

48 Eisenberg PR, Hansbrough JR, Anderson D, Schuster DP. A prospective study of lung water measurements during patient management in an intensive care unit. *American Review of Respiratory Disease* 1987; **136**: 662–668.

49. Falicov RE, Resnekov L. Relationship of the pulmonary artery diastolic pressure to left ventricular end-diastolic and mean filling pressure in patients with and without left ventricular dysfunction. *Circulation* 1970; **42**: 65–73.

50. Fegler G. Measurements of cardiac output in anaesthetized animals by a thermodilution method. *Quarterly Journal of Experimental Physiology* 1954; **39**: 153–164.

51. Feng WC, Singh AK. Management of endobronchial hemorrhage. *Annals of Thoracic Surgery* 1991; **51**: 1045–1046.

52. Fierobe L, Brunet F, Dhainaut JF, Monchi M, Belghith M, Mira JP, Dall'ava Santucci J, Dinh Xuan AT. Effect of inhaled nitric oxide on right ventricular function in adult respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine* 1995; **151**: 1414–1419.

53. Forrester JS, Diamond GJ, Chatterjee K, Swan HJC. Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *New England Journal of Medicine* 1976; **295**: 1356–1362.

54. Forrester JS, Wyatt HL, Da Luz PL, Tyberg JV, Diamond GA, Swan HJC. Functional significance of regional ischemic contraction abnormalities. *Circulation* 1976; **54**: 64–70.

55. Forssmann W. Die Sondierung des Rechten Herzens. *Klinische Wochenschrift* 1929; **8**: 2085–2089.

56. Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991; **83**: 2038–2047

57. Gaar KA, Taylor AE, Jennings Owens L, Guyton AC. Pulmonary capillary pressure and filtration coefficient in the isolated perfused lung. *American Journal of Physiology* 1967; **213**: 910–914.

58. Gaasch WH, Battle WE, Oboler AA, Banas JS, Levine HJ. Left ventricular stress and compliance in men, with special reference to normalized ventricular function curves. *Circulation* 1976; **45**: 746–762.

59. Gardner R, Hollingsworth K Optimizing the electrocardiogram and pressure monitoring. *Critical Care Medicine* 1986; **14**: 651–658.

60. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R. A trial of goal-oriented hemodynamic therapy in critically ill patients. *New England Journal of Medicine* 1995; **333**: 1025–1032.

61. Gibson QH, Roughton FJW. The kinetics and equilibria of the reactions of nitric oxide with sheep haemoglobin. *Journal of Physiology (London)* 1957; **136**: 507–526.

62. Gimosair Y, Sprung CL. The Swan-Ganz catheter. Twenty five years of monitoring. *Critical Care Clinics of North America* 1996; **12**: 771–776.

63. Glauser F Derived pulmonary capillary hydrostatic pressure: Time for clinical application? *Critical Care Medicine* 1991; **19**: 1335–1336.

64. Gnaegi A, Feihl F, Perret C. Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: Time to act? *Critical Care Medicine* 1997; **25**: 213–220.

65. Goldenheim PD, Kazemi H. Cardiopulmonary monitoring of critically ill patients. *New England Journal of Medicine* 1984; **311**: 776–780.

66. Gore J, Goldberg R, Spodick D, Alpert J, Dalen J. A community-wide assessment of the use of pulmonary artery catheters in patients with acute myocardial infarction. *Chest* 1987; **92**: 721–727.

67. Guerrero JE, Munoz J, de la Calle B, Valero R, Alberca MT. Right ventricular systolic time intervals determined by means of a pulmonary artery catheter. *Critical Care Medicine* 1992; **20**: 1529–1536.

68. Guyatt G, Group OIC. A randomized ,control trial of right heart catheterization in critically ill patients. *Journal of Intensive Care Medicine* 1991; **6**: 91–95.

69. Haggmark S, Hohner P, Ostman M, Friedman A, Diamond G, Lowenstein E, Reiz S. Comparison of hemodynamic, electrocardiographic, mechanical, and metabolic indicators of intraoperative myocardial ischemia in vascular surgical patients with coronary artery disease. *Anesthesiology* 1989; **70**: 19–25.

70. Hamilton WF, Moore JW, Kinsman JM, Spurling RG. Simultaneous determination of the greater and lesser circulation times, of the mean velocity of blood flow through the heart and lungs, of the cardiac output and an approximation of the amount of blood actively circulating in the heart and lungs. *American Journal of Physiology* 1928; **85**. 377–378.

71. Hardy JF, Morissette M, Taillefer J, Vauclair R. Pathophysiology of rupture of the pulmonary artery by pulmonary artery balloon-tipped catheters. *Anesthesia and Analgesia* 1993; **62**: 925–930.

72. Hayes M, Timmins A, Yau E, Palazzo M, Hinds C, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *New England Journal of Medicine* 1994; **330**: 1717–1722.

73. Hayes M, Timmins A, Yau E, Palazzo M, Watson D, Hinds C. Oxygen transport patterns in patients with sepsis syndrome or septic shock: Influence of treatment and relationship to outcome. *Critical Care Medicine* 1997; **25**: 926–936.

74. Hayes M, Yau E, Timmins A, Hinds C, Watson D Response of critically ill patients to treatment aimed at achieving supranormal oxygen delivery and consumption. *Chest* 1993; **103**: 886–895.

75. Hellems H, Haynes F, Dexter L. Pulmonary "capillary" pressure in man. *Journal of Applied Physiology* 1949; **2**: 24–29.

76. Herbert WH. Pulmonary artery and left heart end-diastolic pressure relation. *British Heart Journal* 1970; **32**: 774–778.

77 Hinds C, Watson D. Manipulating hemodynamics and oxygen transport in critically ill patients. *New England Journal of Medicine* 1995; **333**: 1074–1075.

78. Hines R. Pulmonary artery catheters: what's the controversy. *Journal of Cardiac Surgery* 1990; **5**: 237–239.

79. Holloway H, Perry M, Downey J, Parker J, Taylor A. Estimation of effective pulmonary capillary pressure in intact lungs. *Journal of Applied Physiology* 1983; **54**: 846–851.

80. Humphrey H, Hall J, Sznajder I, Silverstein M, Wood L. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. *Chest* 1990; **97**: 1176–1180.

81. Hyers TM. ARDS: the therapeutic dilemma. *Chest* 1990; **97**: 1025.

82. Iberti T, Fischer E, Leibowitz A, Panacek E, Silverstein J, Albertson T, Group at PACS. A multicenter study of physicians' knowledge of the pulmonary artery catheter. *Journal of the American Medical Association* 1990; **264**: 2928–2932.

83. Iberti TJ, Benjamin E, Gruppi L, Raskin JM. Ventricular arrhythmias during pulmonary artery catheterization in the intensive care unit Prospective study. *American Journal of Medicine* 1985; **78**: 451–454.

84. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proceedings of the National Academy of Sciences USA* 1987; **84**: 9265–9269.

85. Isaacson IJ, Lowdon JD, Berry AJ, Smith RBD, Knos GB, Weitz FI, Ryan K. The value of pulmonary artery and central venous monitoring in patients undergoing abdominal aortic reconstructive surgery: a comparative study of two selected, randomized groups. *Journal of Vascular Surgery* 1990; **12**: 754–760.

86. Jansen J, Schreuder J, Bogaard J, van Rooyen W, Versprille A. Thermodilution technique for measurement of cardiac output during artificial ventilation. *Journal of Applied Physiology* 1981; **50**: 584–591.

87. Jenkins BS, Bradley RD, Branthwaite MA. Evaluation of pulmonary arterial end-diastolic pressure as an indirect estimate of left atrial mean pressure. *Circulation* 1970; **42**: 75–78.

88 Jiménez Díaz C, Sánchez Cuenca B. El sondaje del corazón derecho. *Archivos de Cardiología y Hematología* 1930; **11**· 105–108.

89. Kandel G, Aberman A. Mixed venous oxygen saturation. its role in the assessment of the critically ill patient. *Archives of Internal Medicine* 1983; **143**: 1400–1402.

90. Katz JD, Cronau LH, Barash PG, Mandel SD. Pulmonary artery flow-guided catheters in the perioperative period: indications and complications. *Journal of the American Medical Association* 1977; **237**: 2832–2834.

91. Kaufman J, Demas C, Stark K, Flancbaum L. Catheter-related septic central venous thrombosis—current therapeutic options. *Western Journal of Medicine* 1986; **145**· 200–203.

92. Kay H, Afshari M, Barash P, Webler W, Iskandrian A, Bemis C, Hakki H, Mundth E. Measurement of ejection fraction by thermodilution techniques. *Journal of Surgical Research* 1983; **34**: 337–346.

93. Kearney TJ, Shabot MM. Pulmonary artery rupture associated with the Swan-Ganz catheter. *Chest* 1995; **108:** 1349–1352.
94. Klein O. Zur Bestimmung des zirkulatorischen minutens Volumen nach dem Fickschen Prinzip. *Munchen Medizin Wochenschrift* 1930; **77:** 1311.
95. Knobel E, Fernandes C, Akamine N. Right ventricular influence on left ventricular performance in septic patients. *Critical Care Medicine* 1987; **15:** 1158–1159.
96. Kollef MH, Schuster DP. The acute respiratory distress syndrome. *New England Journal of Medicine* 1995; **332:** 27–37.
97. Komadina K, Schenk D, LaVeau P, Duncan C, Chanbers S. Interobserver variability in the interpretation of pulmonary artery catheter pressure tracings. *Chest* 1991; **100:** 1647–1654.
98. Kubo S, Burchenal J, Cody R. Comparison of direct Fick and thermodilution cardiac output techniques at high flow rates. *American Journal of Cardiology* 1987; **9:** 384–386.
99. Lagerloef H, Werkoe L. Studies on the circulation of blood in man. VI. The pulmonary capillary venous pressure pulse in man. *Scandinavian Journal of Clinical and Laboratory Investigation* 1949; **1:** 147–161.
100. Lappas D, Lell WA, Gabel JC, Civetta JM, Lowenstein E. Indirect measurement of left-atrial pressure in surgical patients—pulmonary-capillary wedge and pulmonary-artery diastolic pressures compared with left-atrial pressure. *Anesthesiology* 1973; **38:** 394–397.
101. Lategola M, Rahn H. A self-guiding catheter for cardiac and pulmonary arterial catheterization and occlusion. *Proceedings of the Society for Experimental Biology and Medicine* 1953; **84:** 667–668.
102. Levy MM. Pulmonary capillary pressure. Clinical implications. *Critical Care Clinics* 1996; **12:** 819–839.
103. Lewis FR, Elings VB, Hill SL, Christensen JM. The measurement of extravascular lung water by thermal-green dye indicator dilution. *Annals of the New York Academy of Science* 1982; **384:** 394–410.
104. Light LH. Non-injurious ultrasonic technique for observing flow in the human aorta. *Nature (London)* 1969; **224:** 1119–1121.
105. Linton R, Band D, O'Brien T, Jonas M, Leach R. Lithium dilution cardiac output measurement: A comparison with thermodilution. *Critical Care Medicine* 1997; **25:** 1796–1806.
106. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One. *American Journal of Respiratory and Critical Care Medicine* 1994; **150:** 833–52.
107. Mangano DT, Browner W, Hollenberg M, London MJ, Tubau JF, Tateo IM, Group SR. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. *New England Journal of Medicine* 1990; **323:** 1781–1788.
108. Mangano DT, Goldman L. Preoperative assessment of cardiac patients with known or suspected coronary disease. *New England Journal of Medicine* 1995; **333:** 1759–1756.
109. Marini JJ, Culver BH, Butler J. Mechanical effect of lung distension with positive pressure on cardiac function. *American Review of Respiratory Disease* 1981; **124:** 382–384.
110. Martin W, Cheung P, Johnson C, Wong M. Continuous monitoring of mixed venous oxygen saturation in man. *Anesthesia and Analgesia* 1973; **52:** 784–793.
111. Matthay MA, Wiener Kronish JP. Intact epithelial barrier function is critical for the resolution of alveolar edema in humans. *American Review of Respiratory Disease* 1990; **142:** 1250–1257.
112. Mermel LA, Maki DG. Infectious complications of Swan-Ganz pulmonary artery catheters. Pathogenesis, epidemiology, prevention, and management. *American Journal of Respiratory and Critical Care Medicine* 1994; **149:** 1020–1036.
113. Mihaljevic T, von Segesser LK, Tonz M, Leskosek B, Seifert B, Jenni R, Turina M. Continuous versus bolus thermodilution cardiac output measurements—a comparative study. *Critical Care Medicine* 1995; **23:** 944–949.
114. Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *American Review of Respiratory Disease* 1992; **145:** 990–998.
115. Moncada S, Higgs EA. Mechanism of disease: the l-arginine–nitric oxide pathway. *New England Journal of Medicine* 1993; **329:** 2002–2012.
116. Moser KM, Auger WR, Fedullo PF. Chronic major-vessel thromboembolic pulmonary hypertension. *Circulation* 1990, **81:** 1735–1743.
117. Nadeau S, Noble W. Misinterpretation of pressure measurements from the pulmonary artery catheter. *Canadian Anaesthetists' Society Journal* 1986; **33:** 352–363.
118. Nehme A. Swan-Ganz catheter: comparison of insertion technique. *Archives of Surgery* 1980; **115:** 1194–1196.
119. Nelson L. Continuous venous oximetry in surgical patients. *Annals of Surgery* 1986; **203:** 329–333
120. Nelson LD. The new pulmonary arterial catheters. Right ventricular ejection fraction and continuous cardiac output. *Critical Care Clinics* 1996; **12:** 795–818.
121. Nisikawa T, Dohi S. Errors in the measurement of cardiac output by thermodilution. *Canadian Journal of Anaesthesia* 1993; **40:** 142–153.
122. O'Quin D, Marini J. Pulmonary artery occlusion pressure. clinical physiology, measurement, and interpretation. *American Review of Respiratory Disease* 1983; **128:** 319–326.
123. Palmer RMJ, Ashton DS, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. *Nature (London)* 1988; **333:** 664–666.
124. Paterson S, Starling EH. On the mechanical factors which determine the output of the ventricles. *Journal of Physiology (London)* 1914; **48:** 357.
125. Pavek E, Pavek K, Boska D. Mixing and observation errors in indicator-dilution studies. *Journal of Applied Physiology* 1970; **28:** 733–740.
126. Pearl RG. Inhaled nitric oxide. The past, the present, and the future. *Anesthesiology* 1993, **78:** 413–416
127. Pepke Zaba J, Higenbottam TW, Dinh Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet* 1991; **338:** 1173–1174.
128. Pinsky MR. The role of the right ventricle in determining cardiac output in the critically ill. *Intensive Care Medicine* 1993; **19:** 1–2.
129. Pulmonary artery catheter consensus conference participants Pulmonary artery catheter consensus conference: consensus statement. *Critical Care Medicine* 1997; **25:** 910–925.
130. Puybasset L, Rouby JJ, Mourgeon E, Stewart TE, Cluzel P, Arthaud M, Poete P, Bodin L, Korinek AM, Viars P. Inhaled nitric oxide in acute respiratory failure: dose–response curves. *Intensive Care Medicine* 1994; **20:** 319–327
131. Puybasset L, Stewart T, Rouby JJ, Cluzel P, Mourgeon E, Belin MF, Arthaud M, Landault C, Viars P. Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with acute respiratory distress syndrome. *Anesthesiology* 1994; **80:** 1254–1267.
132. Quinn AC, Petros AJ, Vallance P. Nitric oxide: an endogenous gas. *British Journal of Anaesthesia* 1995; **74:** 443–451
133. Rahimtoola SH, Loeb HS, Ehsani A, Sinno MZ, Chuquimia R, Lal R. Relationship of pulmonary artery to left ventricular diastolic pressures in acute myocardial infarction *Circulation* 1972; **46:** 283–290.
134. Rao TL, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. *Anesthesiology* 1983; **59:** 499–505.
135. Redl G, Germann P, Plattner H, Hammerle A Right ventricular function in early septic shock states. *Intensive Care Medicine* 1993; **19:** 3–7.
136. Reinhart K, Radermacher P, Sprung CL, Phelan D, Bakker J, Steltzer H. PA catheterization—quo vadis? Do we have to change the current practice with this monitoring device. *Intensive Care Medicine* 1997; **23:** 605–609.
137. Renner L, Morton M, Sakuma G. Indicator amount, temperature, and intrinsic cardiac output affect thermodilution cardiac output accuracy and reproducibility. *Critical Care Medicine* 1993; **21:** 586–597
138. Reuse C, Vincent JL, Pinsky MR. Measurements of right ventricular volumes during fluid challenge. *Chest* 1990; **98:** 1450–1454.
139. Robin E. Death by pulmonary artery flow-directed catheter. Time for a moratorium? *Chest* 1987; **92:** 727–731.
140. Robin ED. The cult of the Swan-Ganz catheter. Overuse and abuse of pulmonary flow catheters. *Annals of Internal Medicine* 1985; **103:** 445–449.
141. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *New England Journal of Medicine* 1993; **328:** 399–405.
142. Rowley K, Clubb K, Walker-Smith G, Cabin H. Right sided infective endocarditis as a consequence of flow-directed pulmonary artery catheterization. *New England Journal of Medicine* 1984; **311:** 1152–1156.

143. Rubin LJ. Primary pulmonary hypertension. *Chest* 1993; **104**: 236–250.
144. Safcak K, Nelson LD, Cheatham M. Pressure vs volume predictions of ventricular preload in patients with pulmonary hypertension (PHTN). *Critical Care Medicine* 1994; **22**: A102.
145. Salvaterra CG, Rubin LJ. Investigation and management of pulmonary hypertension in chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 1993; **148**: 1414–1417.
146. Santacana E, Litvan H, Aris A, Montiel J, Villar Landeira JM. Massive endobronchial hemorrhage due to pulmonary artery rupture caused by a Swan-Ganz catheter. *Revista Española de Anestesiologia y Reanimación* 1993; **40**: 230–233.
147. Schuller D, Mitchell JP, Calandrino FS, Schuster DP. Fluid balance during pulmonary edema. Is fluid gain a marker or a cause of poor outcome? *Chest* 1991; **100**: 1068–1075.
148. Schulman DS, Biondi JW, Matthay RA, Zaret BL, Soufer R. Differing responses in right and left ventricular filling, loading and volumes during positive end-expiratory pressure. *American Journal of Cardiology* 1989; **64**: 772–777.
149. Schuster DP. ARDS: clinical lessons from the oleic acid model of acute lung injury. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: 245–260.
150. Schuster DP. Fluid management in ARDS: "keep them dry" or does it matter? *Intensive Care Medicine* 1995; **21**: 101–103.
151. Scudeni P, Prough D, Price J, Comer P. Cessation of pulmonary artery catheter induced endobronchial hemorrhage associated with the use of PEEP. *Anesthesia and Analgesia* 1983; **62**: 236–238.
152. Shackman R, Graber G, Melrose D. Hemodynamics of the surgical patient under general anesthesia. *British Journal of Surgery* 1952; **40**: 193–201.
153. Shah KB, Rao TLK, Laughlin S, El-Etr AA. A review of pulmonary artery catheterization in 6,245 patients. *Anesthesiology* 1984; **61**: 271–275
154. Shasby DM, Dauber IM, Pfiister S. Swan-Ganz catheter location and left atrial pressure determine the accuracy of the wedge pressure when positive end-expiratory pressure is used. *Chest* 1981; **80**: 666–670.
155. Shoemaker W. Hemodynamic patterns after acute anesthetized and unanesthetized trauma. *Archives of Surgery* 1967; **95**: 492–499.
156. Shoemaker W, Appel P, Kram H, Waxman K, Lee T. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988; **94**: 1176–1186.
157. Shoemaker W, Kram H, Appel L, Fleming W. The efficacy of central venous and pulmonary artery catheters and therapy based upon them in reducing mortality and morbidity *Archives of Surgery* 1990; **125**: 1332–1338.
158. Shoemaker W, Montgomery E, Kaplan E, Elwyn D. Physiologic patterns in surviving and nonsurviving shock patients. *Archives of Surgery* 1973; **106**: 630–636.
159. Sibbald WJ, Driedger AA, Myers ML, Short AI, Wells GA. Biventricular function in the adult respiratory distress syndrome. *Chest* 1983; **84**: 126–134.
160. Siegl L, Pearl R, Shafer S. The longitudinal distribution of pulmonary vascular resistance during unilateral hypoxia. *Anesthesiology* 1989; **70**: 527–532.
161. Singer M, Clarke J, Bennett ED. Continuous hemodynamic monitoring by esophageal Doppler. *Critical Care Medicine* 1989; **17**: 447–452.
162. Sivak ED, Wiedemann HP. Clinical measurement of extravascular lung water. *Critical Care Clinics of North America* 1986; **2**: 511–526.
163. Snider M, Ric M, Bingham J. Right ventricular performance in ARDS. Radionuclide scintiscan and thermal dilution studies. *American Review of Respiratory Disease* 1980; **121**: 192.
164. Soni N. Swan song for the Swan-Ganz catheter? *British Medical Journal* 1996; **313**: 763–764.
165. Spinale FG, Zellner JL, Mukherjee R, Ferris SE, Crawford FA. Thermodilution right ventricular ejection fraction. Catheter positioning effects. *Chest* 1990; **98**: 1259–1265.
166. Sprung CL, Rackow EC, Fein IA, Jacob AI, Isikoff SK. The spectrum of pulmonary edema: differentiation of cardiogenic, intermediate, and noncardiogenic forms of pulmonary edema. *American Review of Respiratory Disease* 1981; **124**: 718–722.
167. Starling E. On absorption of fluids from connective tissue spaces. *Journal of Applied Physiology* 1896; **19**: 312.
168. Stewart GN. Researches on the circulation time and on the influences which affect it. IV. The output of the heart. *Journal of Physiology (London)* 1897; **22**. 159–173.
169. Swan H, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with use of a flow-directed balloon tipped catheter. *New England Journal of Medicine* 1970; **283**: 447–451.
170. Swan HJC, Ganz W. Hemodynamic measurements in clinical practice: a decade in review. *Journal of the American College of Cardiology* 1983; **1**: 103–113.
171. Synder J. Cardiac output and oxygen consumption of nine surgical patients before and after operation. *Journal of Clinical Investigation* 1938; **17**: 571–579.
172. Sznajder JI, Wood LD. Beneficial effects of reducing pulmonary edema in patients with acute hypoxemic respiratory failure. *Chest* 1991; **100**: 890–892.
173. Townsley MI, Korthuis RJ, Rippe B, Parker JC, Taylor AE. Validation of double vascular occlusion method for $P_{c,i}$ in lung and skeletal muscle. *Journal of Applied Physiology* 1986; **61**: 127–132.
174. Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. *Chest* 1992; **102**: 216–220.
175. Tuman K, McCarthy R, Spiess B, DaValle M, Hompland S, Dabir R, Ivankovich A. Effect of pulmonary artery catheterization on outcome in patients undergoing coronary artery surgery. *Anesthesiology* 1989; **70**: 199–206.
176. Tuman KJ, Roizen MF. Outcome assessment and pulmonary artery catheterization: why does the debate continue? *Anesthesia and Analgesia* 1997; **84**: 1–4.
177. Urschel JD, Myerowitz PD. Catheter-induced pulmonary artery rupture in the setting of cardiopulmonary bypass. *Annals of Thoracic Surgery* 1993; **56**: 585–389.
178. van Daele ME, Sutherland GR, Mitchell MM, Fraser AG, Prakash O, Rulf EN, Roelandt JR. Do changes in pulmonary capillary wedge pressure adequately reflect myocardial ischemia during anesthesia? A correlative preoperative hemodynamic, electrocardiographic, and transesophageal echocardiographic study. *Circulation* 1990; **81**: 865–871.
179. Van Grondelle A, Ditchey R, Groves B. Thermodilution method overestimates low cardiac output in humans. *American Journal of Physiology* 1983; **245**: H690–H692.
180. Viquerat CE, Righetti A, Suter PM. Biventricular volumes and function in patients with adult respiratory distress syndrome ventilated with PEEP. *Chest* 1983; **83**: 509–514.
181. Waller J, Kaplan J, Bauman D, Craver J. Clinical evaluation of a new fiberoptic catheter oximeter during cardiac surgery. *Anesthesia and Analgesia* 1982; **61**: 676–679.
182. Weed HG. Pulmonary "capillary" wedge pressure not the pressure in the pulmonary capillaries. *Chest* 1991; **100**: 1138–1140.
183 Weisel R, Berger R, Hechtman H. Measurement of cardiac output by thermodilution. *New England Journal of Medicine* 1975; **292**: 682–684.
184. Weissel W, Salzmann F, Vetter H. Pulmonary capillary arterial pressure pulse in man. *British Heart Journal* 1951; **14**: 47–52.
185. Wessel H, Paul M, James G, Grahn A. Limitations of thermal dilution curves for cardiac output determinations. *Journal of Applied Physiology* 1971; **30**: 643–652.
186. West J. *Respiratory Physiology. The Essentials.* Baltimore: Waverly Press, 1979
187. Widemann HP. Wedge pressure in pulmonary veno-occlusive disease. *New England Journal of Medicine* 1986; **315**: 1233.
188. Wiedemann HP, Matthay MA, Matthay RA. Cardiovascular–pulmonary monitoring in the intensive care unit (part 1). *Chest* 1984; **85**: 537–549.
189. Yelderman ML, Ramsay MA, Quinn MD, Paulsen AW, McKown RC, Gillman PH. Continuous thermodilution cardiac output measurement in intensive care unit patients. *Journal of Cardiothoracic and Vascular Anesthesia* 1992; **6**: 270–274.
190. Yu M, Levy M, Smith P, Takiguchi S, Miyasaki A, Myers S. Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: A prospective, randomized, controlled study. *Critical Care Medicine* 1993; **21**: 830–838.
191. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. *New England Journal of Medicine* 1977; **296**: 476–480.
192. Zion M, Balkin J, Rosenmann D, Goldbourt U, Reicher-Reiss H, Kaplinsky E, Behar S. Use of pulmonary artery catheters in patients with acute myocardial infarction Analysis of experience in 5,841 patients in the SPRINT registry. *Chest* 1990; **98**: 1331–1335.

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SHORT COMMUNICATIONS

Cerebrospinal fluid concentrations of propofol during anaesthesia in humans

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J. Ahlner and C. Eintrei

Summary

The concentration of propofol in and surrounding the human brain during propofol anaesthesia is unknown. We measured simultaneously the concentration of propofol in cerebrospinal fluid (CSF) from an indwelling intraventricular catheter and the concentration in arterial blood in five neurosurgical patients before, during induction (at 2.5 and 5 min) and during a maintenance propofol infusion (at 15 and 30 min). After induction of anaesthesia with propofol 2 mg kg^{-1}, anaesthesia was maintained with an infusion of 8 mg kg^{-1} h^{-1} for 15 min and then reduced to 6 mg kg^{-1} h^{-1}. The plasma concentration of propofol increased rapidly during induction and reached a plateau concentration of mean 2.24 (SD 0.66) µg ml^{-1} after 5 min. The concentration of propofol in CSF showed a slower increase during induction and remained almost constant at 35.5 (19.6) ng ml^{-1} at 15–30 min after induction. The CSF concentration of propofol that we measured was 1.6% of the plasma concentration and consistent with the high protein binding of the drug in plasma. (*Br. J. Anaesth.* 1998; **81**: 957–959)

Keywords: anaesthetics i.v., propofol, cerebrospinal fluid.

The invasive techniques required to study the distribution of propofol in the brain have limited such studies to animal models. Hence, the concentration of propofol in and surrounding the cells of the human brain during clinical anaesthesia is unknown. Knowledge of this concentration is useful for delineating the molecular and cellular mechanisms of propofol anaesthesia. Previous *in vitro* studies investigating the intracellular effects of propofol and its action on the GABA$_A$ receptor have used a wide range of propofol concentrations to mimic the effects of clinical anaesthesia. Further, a dose-dependent action of propofol on GABA$_A$ receptors of hypothalamic neurones have been observed, with low concentrations (0.1–100 µmol litre^{-1}) potentiating GABA$_A$ receptors and higher concentrations (1 µmol litre^{-1}–1 mmol litre^{-1}) producing activation of GABA-evoked currents.[1]

Neurosurgical patients with an indwelling intraventricular catheter offer a unique setting in which to investigate the distribution of propofol in cerebrospinal fluid (CSF) during propofol anaesthesia. In this study we have measured the concentration of propofol in CSF during induction and a maintenance propofol infusion, and related this to plateau arterial blood concentrations measured simultaneously.

Methods and results

The study was approved by the Ethics Committee of Linköping University Hospital and patients or their relatives gave informed consent. We studied five neurosurgical patients undergoing general anaesthesia who also had an indwelling intraventricular drain without any signs of active bleeding into the subarachnoid space. Three of the patients had suffered a subarachnoid haemorrhage, one a cerebellar haemorrhage and one had sustained major craniofacial trauma. The study group was comprised of four males and one female, with a mean age of 60.2 (range 26–77) yr. In three of the patients the trachea was already intubated before the start of the study and propofol anaesthesia was superimposed on ongoing sedation with midazolam for change of the tracheal tube. The two other patients were awake at the start of anaesthesia and tracheal intubation was conducted in a standard fashion. Before induction of anaesthesia a radial artery catheter was inserted in all patients through which blood samples were collected and systemic arterial pressure monitored.

After pretreatment with fentanyl 1 µg kg^{-1}, anaesthesia was induced with propofol (Diprivan 1%) 2 mg kg^{-1} i.v. over 2 min. Loss of the eyelash reflex was chosen as a pharmacodynamic end-point during induction. Anaesthesia was maintained with a continuous infusion of propofol commenced 5 min after the start of induction at an initial infusion rate of 8 mg kg^{-1} h^{-1} and then reduced to 6 mg kg^{-1} after 15 min. Neuromuscular block was facilitated with pancuronium 0.1 mg kg^{-1}. Systemic hypotension was defined as a mean arterial pressure of <70 mm Hg and was treated with incremental doses of ephedrine. In all patients the lungs were ventilated to normocapnia during the study to minimize the confounding effects of arterial carbon dioxide partial pressures on cerebral blood flow and intracranial pressure. The partial pressure of carbon dioxide in arterial blood was monitored indirectly using capnography and directly by serial blood-gas measurements.

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The CSF samples were obtained from an indwelling Holter intraventricular catheter (Codman Medes SA) positioned in one of the frontal horns. The deadspace of the catheter and sampling system is 0.4 ml, and 0.8 ml was withdrawn before the CSF samples proper were obtained. Arterial blood and cerebrospinal fluid samples (5 ml) were collected simultaneously before induction of anaesthesia, after the start of induction (at 2.5 and 5 min) and during continuous infusion (at 15 and 30 min). The samples were collected and stored in glass containers at −70°C until the propofol assay was performed. Propofol concentrations in CSF and plasma were measured by high-performance liquid chromatography and fluorescence detection using minor modifications, as described previously.[2]

Plasma and CSF concentrations of propofol at 2.5, 5, 15 and 30 min are shown in figure 1. After a rapid increase in plasma concentrations of propofol, plateau concentrations in plasma were observed at 5–30 min. The concentration of propofol in CSF increased slowly for 15 min after induction. At 15–30 min there was little variation in CSF propofol concentration.

The time interval between 5 and 30 min represents the period during which we observed a plateau concentration in plasma. Mean propofol concentration in plasma during this interval was 2.24 (SD 0.66, SEM 0.29) μg ml^{-1} and that in CSF 35.5 (SD 19.6, SEM 8.9) ng ml^{-1}. The ratio of propofol in CSF to that in plasma during the plateau phase was 0.016 (1.6%).

Comment

We have demonstrated that the CSF concentration of propofol was 1.6% of the plateau plasma concentration. Propofol has a short distribution half-life of 2 min[3] and it is likely that the plateau concentration in arterial blood we observed during the maintenance infusion represents a pseudo-steady-state. Under such conditions, propofol equilibrates between arterial blood and CSF. The 60-fold difference in the concentration of propofol between CSF and plasma is consistent with the high plasma protein binding of propofol (97–99%).[3] Only the free or unbound fraction enters and equilibrates with CSF across the choroid plexus and its ability to penetrate the choroidal epithelia is a function of its lipophilicity and the degree of ionization at body pH.[4]

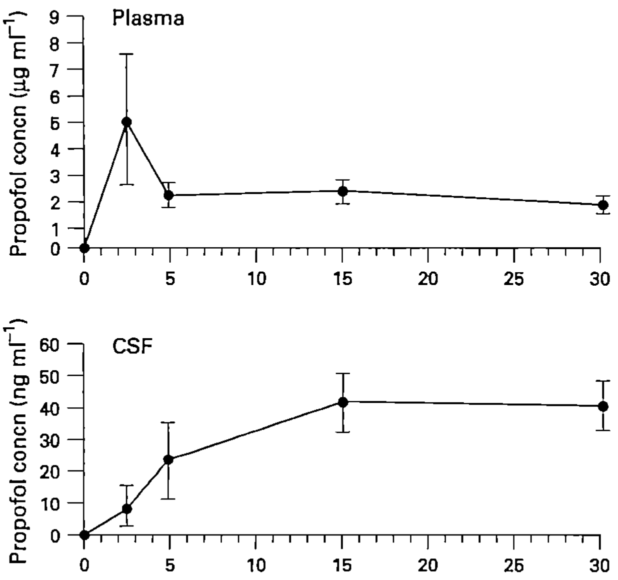

Figure 1 Propofol concentrations in plasma and CSF over time (mean (SEM)).

Cerebral blood flow determines the rate at which a drug is delivered to the effect site or biophase and there is a general assumption that the rate of uptake into the CSF and brain of highly lipophilic drugs such as propofol is flow-limited. It is possible therefore, that a reduction in cerebral perfusion pressure and cerebral blood flow induced by an anaesthetic agent may limit its own biophase distribution. We maintained systemic arterial pressures throughout the study in order to eliminate the effects of this phenomenon. Nevertheless, some of the patients can be expected to have had regional disturbances of cerebral blood flow secondary to their intracranial pathology and this could explain, in part, the inter-patient variation in CSF concentrations of propofol. The rate of uptake of drugs into CSF is also influenced by the permeability of the blood–CSF barrier, and increased permeability characterizes many pathological conditions, including stroke, subarachnoid haemorrhage, seizures, trauma, ischaemia and systemic hypertension.[5] It seems difficult therefore, to explain the overall low concentrations of propofol in the CSF of our patients by virtue of blood flow disturbances or impaired transfer of propofol across the blood–CSF barrier.

The normal rate of CSF production has been estimated to be 0.5 ml min^{-1}. During the study we sampled a greater volume of CSF than that produced and this may have affected the measured propofol concentrations. However, we observed relatively constant CSF concentrations in the face of a plateau blood concentration during the maintenance propofol infusion. CSF was sampled via an intraventricular catheter positioned in one of the frontal horns of the brain and thus represents the propofol concentration from the central parts of the CSF compartment. While pooling of ventricular CSF is known to occur, it is assumed that the CSF drains into the catheter rather than following the normal drainage or storage routes where resistance is increased in patients with subarachnoid haemorrhage. Similarly, subarachnoid haemorrhage is associated with a reduced CSF production rate,[6] which would not account for the CSF propofol concentrations we observed.

In summary, the concentrations of propofol in CSF that we demonstrated were consistent with its physicochemical properties, and were considerably less than the concentrations previously assumed to surround the brain during propofol anaesthesia in humans. Our findings suggest that the generally accepted range of propofol concentrations acting on neurones and the GABA$_A$ receptor may not be relevant to the clinical setting.

References

1. Adodra S, Hales TG. Potentiation, activation and blockade of GABA$_A$ receptors of clonal murine hypothalamic GT1-7 neurones by propofol. *British Journal of Pharmacology* 1995; 115: 953–960.
2. Mazzi G, Schinella M. Simple and practical high-performance liquid chromatographic assay of propofol in human blood by phenyl column chromatography with electrochemical detection. *Journal of Chromatography* 1990; 528: 537–541

3. Servin F, Desmonts JM, Haberer JP, Cockshott ID, Plummer GF, Farinotti R. Pharmacokinetics and protein binding of propofol in patients with cirrhosis. *Anesthesiology* 1988; **69**: 887–891.
4. Brodie BB, Kurz H, Schanker LS. The importance of dissociation constant and lipid-solubility influencing the passage of drugs into the cerebrospinal fluid. *Epilepsia* 1960; **130**: 20–27.
5. Fishman RA. Blood–brain barrier. In: Mills LE, ed. *Cerebrospinal Fluid in Diseases of the Nervous System* Philadelphia: WB Saunders, 1980, 43–75.
6. Kosteljanetz M. CSF-dynamics in patients with subarachnoid and/or intraventricular haemorrhage. *Journal of Neurosurgery* 1984; **60**. 940–946.

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Recovery after halothane anaesthesia induced with thiopental, propofol–alfentanil or halothane for day-case adenoidectomy in small children

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Summary

We studied recovery from halothane anaesthesia in 93 children, aged 1–3 yr, undergoing day-case adenoidectomy. Children were allocated randomly to receive thiopental 5 mg kg^{-1} (group TH), alfentanil 10 µg kg^{-1} and propofol 3 mg kg^{-1} (group PAH) or 5% halothane (group HH) for induction of anaesthesia. In group TH, tracheal intubation was facilitated with succinylcholine (suxamethonium) 1.5 mg kg^{-1}. In groups PAH and HH, tracheal intubation was performed without neuromuscular block, and succinylcholine was used only if required. Anaesthesia was maintained with 1–3% halothane during spontaneous respiration. Times to achieving predetermined recovery end-points were recorded. Quality of recovery was assessed using a score of 1–9 (best to worst) for sedation, crying, restlessness and agitation. A postoperative questionnaire was used to determine the well-being of the child at home, 24 h after operation. Emergence from anaesthesia (response to non-painful stimuli) occurred earlier in group HH (mean 9 (SD 6) min) than in groups PAH (13 (6) min, $P<0.01$) and TH (18 (14) min, $P<0.01$). Sitting up, walking and home readiness were achieved earlier in groups PAH and HH than in group TH ($P<0.05$ for each variable). Children in group TH were more sedated during the first 30 min after anaesthesia than those in the two other groups ($P<0.05$) while emergence-related delirium was more common in group HH than in group TH ($P<0.01$). Well-being at home was similar in all groups. We conclude that induction of halothane anaesthesia with propofol–alfentanil or halothane provided more rapid recovery and earlier discharge than that with thiopental. (*Br. J. Anaesth.* 1998; **81**: 960–962)

Keywords: anaesthesia, paediatric; anaesthetics i.v., propofol; anaesthetics i.v., thiopental; anaesthetics volatile, halothane; recovery, postoperative; surgery, paediatric

Children aged 1–3 yr form a common group of patients undergoing short day-case procedures. The anaesthetic used should have minimal postoperative side effects to ensure rapid recovery from anaesthesia and return to a normal routine at home.

Propofol is a short-acting i.v. anaesthetic which, as an induction or maintenance agent, provides rapid recovery from anaesthesia.[1] However, rapid recovery does not necessarily shorten the time to discharge.[1] Further, duration of anaesthesia may override the benefit gained from propofol as an induction agent, making recovery more dependent on the maintenance agent.[2]

Few studies have investigated recovery after propofol-induced anaesthesia in children less than 3 yr. We decided to compare the recovery profile, after halothane anaesthesia, of an induction dose of propofol with two conventional induction agents, thiopental and halothane, in children aged 1–3 yr undergoing day-case adenoidectomy.

Methods and results

After obtaining approval from the local Hospital Ethics Committee and written informed consent from parents, we studied 93 children, ASA I–II, aged 1–3 yr, undergoing day-case adenoidectomy. No premedication was used. Each child was allocated randomly to one of three groups using a computer-generated random number table: group TH (n=31) received thiopental 5 mg kg^{-1}; group PAH (n=31) received propofol 3 mg kg^{-1} and alfentanil 10 µg kg^{-1} (60 s before propofol); and group HH (n=31) 5% inspired halothane for induction of anaesthesia. In group TH, tracheal intubation was facilitated with succinylcholine 1.5 mg kg^{-1}. In groups PAH and HH, tracheal intubation was performed without neuromuscular block, and succinylcholine 1.5 mg kg^{-1} was given only if required. In all groups, anaesthesia was maintained with 1–3% halothane and 70% nitrous oxide in oxygen delivered via a Bain co-axial breathing system with the child breathing spontaneously. All children received diclofenac 12.5 mg rectally after tracheal intubation. Standard monitoring was used throughout anaesthesia.

In the recovery room, the recovery and behaviour of the children were assessed by the same nurse, who was unaware of the induction method used. Sedation, crying, restlessness (motor activity) and agitation were evaluated using an open scale scoring from 1–9 (best to worst). Scores were recorded at 10-min intervals for the first hour and then every 30

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min until discharge. If the child at any point of evaluation scored six or more for crying, restlessness or agitation, recovery from anaesthesia was considered delirious. Repeated doses of pethidine 5 mg i.v. were given for postoperative pain relief at the discretion of the recovery nurse. Times to achieving the following predetermined recovery end-points were measured (from discontinuation of halothane): (1) time to responding to non-painful stimuli (emergence time); (2) time to first dose of pethidine; (3) time to sitting up; (4) time to drinking; (5) time to walking; and (6) time taken to achieve the criteria for discharge from the recovery room, which were stable vital signs for at least 30 min, able to walk according to age, tolerance of clear fluids, no nausea or vomiting, and no pain.

A postoperative questionnaire was given to parents to be completed at home. Parents were asked to record the well-being and behaviour of the child (tiredness, eating, drinking ability, sleeping, vomiting, pain) until 24 h after discharge.

Analyses were performed using one-way analysis of variance (ANOVA) with Bonferroni's correction, Mann Whitney *U* test and chi-square test where appropriate. $P<0.05$ was considered significant. Data are presented as mean (SD) or number (%). In order to detect a 20-min difference in discharge time with a mean value of 100 min (SD 25 min), 25 patients were required in each group. This gave the study a power of 80% at a=0.05.

The three groups were comparable in age, weight, duration of anaesthesia and surgery. Mean duration of anaesthesia was 22 (5), 24 (7) and 23 (6) min in groups TH, PAH and HH, respectively (ns). Tracheal intubation was successful in all patients in groups TH and HH. Seven patients in group PAH were given succinylcholine to facilitate tracheal intubation. The mean dose of rectal diclofenac was 0.95–0.98 mg kg^{-1} in the different groups (ns). Time to achieve recovery end-points are shown in table 1. Children in group PAH were more sedated than those in group HH at 10 min after anaesthesia ($P<0.01$). Children in group TH were more heavily sedated during the first 30 min and at 60 and 90 min after anaesthesia compared with children in groups PAH and HH ($P<0.05$ at each time). The incidence of emergence-related delirium was 7%, 23% and 29% in groups TH, PAH and HH, respectively ($P<0.01$ group TH *vs* HH, $P<0.07$ group TH *vs* PAH). The mean dose of pethidine did not differ between groups but time to administering the first dose was significantly shorter in group HH (11 (9) min) than in group TH (19 (13) min) ($P<0.01$). Postoperative vomiting in the recovery room occurred in 16%, 10% and 10% of patients in groups TH, PAH and HH, respectively (ns). At home, the well-being and recovery of the children were similar in all groups.

Table 1 Recovery times (min) from the end of anaesthesia in the three groups (mean (SD) and 95% confidence intervals (CI)). *$P<0.05$ *vs* the two other groups (Mann–Whitney *U* test)

	Group TH (*n*=31)	Group PAH (*n*=31)	Group HH (*n*=31)
Emergence	18 (14)	13 (6)	9 (6)*
	13–23	10–14	7–11
Sitting	63 (24)*	50 (25)	43 (22)
	52–71	40–60	35–51
Drinking	81 (25)	69 (25)	71 (26)
	71–91	59–79	61–80
Walking	118 (31)*	92 (31)	89 (23)
	108–128	80–103	80–98
Discharge	132 (29)*	112 (31)	108 (22)
	121–142	100–123	100–116

Comment

Our findings differed from two previous studies investigating recovery after halothane anaesthesia induced with propofol, thiopental or halothane in children older than 3 yr.[1 2] Aun and colleagues found no differences in early recovery characteristics (open eyes on command, full Steward score) between induction agents.[2] Our results support the suggestion that as the duration of anaesthesia increases, recovery becomes more dependent on the maintenance agent rather than on the induction agent.[2] The short duration of anaesthesia in our study (<25 min) allowed both i.v. induction agents to have a residual effect in the early recovery period, thus explaining the slower awakening (emergence) in the thiopental and propofol–alfentanil groups compared with the halothane group. Further, the longer redistribution half-life of thiopental (43 min)[3] compared with propofol (26 min)[4] resulted in higher scores for sedation for a longer period after anaesthesia in the thiopental group.

The use of alfentanil in the propofol–alfentanil group may have prolonged time to emergence. However, although emergence was fastest in the halothane group, children in the propofol–alfentanil group did not differ from those in the halothane group for any of the other recovery variables. This probably reflects the rapid clearance of propofol[4] and alfentanil[5] in children.

The short duration of anaesthesia in our study could also explain why the use of no i.v. induction agent provided the fastest emergence and rapid recovery from anaesthesia. Failure of several tissues to reach equilibration with the alveolar anaesthetic partial pressure during a short anaesthetic would result in more rapid elimination of halothane after discontinuation.[6] Hanallah and colleagues found that early recovery (full Steward score) from anaesthesia induced with halothane did not differ from thiopental.[1] Our results could be explained by the longer duration of anaesthesia (>80 min) in their study.

More children experienced "delirious recoveries" (crying, restlessness and agitation) in the halothane group compared with the thiopental group. Time to peak blood concentration after rectal diclofenac was 30 min[7] which, for some children, would have occurred 10–15 min after anaesthesia. Rapid emergence from anaesthesia may have led to the delirious recoveries through early perception of pain and could account for the significantly earlier administration of analgesics in the halothane group. The reduced incidence of emergence delirium and later administration of pethidine in the propofol–alfentanil group could be a result of the analgesic effect of alfentanil extending into the immediate recovery period.[5]

Time to home readiness was similar in both the propofol–alfentanil and halothane groups, being significantly shorter than in the thiopental group. Later administration of pethidine in the thiopental group may have caused residual sedation, which is reflected in the higher sedation scores at 60 and 90 min after anaesthesia. Also, more children vomited at a later stage in the thiopental group, which prolonged discharge time in some children.

In summary, we conclude that i.v. induction with propofol–alfentanil and inhalation induction with halothane provided similar rapid recovery characteristics after maintenance of anaesthesia with halothane. The only difference between the two groups was shorter emergence time and lower sedation scores during the first 10 min after the end of anaesthesia in the halothane group. Induction with thiopental resulted in significantly slower recovery after anaesthesia compared with the two other groups, but recovery at home was not affected by the induction agent.

References

1. Hanallah RS, Britton JT, Schafer PG, Patel RI, Norden JM. Propofol anaesthesia in paediatric ambulatory patients: a comparison with thiopentone and halothane. *Canadian Journal of Anaesthesia* 1994; **41**: 12–18.
2. Aun CST, Short TG, O'Meara ME, Leung DHY, Rowbottom YM, Oh TE. Recovery after propofol infusion anaesthesia in children: comparison with propofol, thiopentone or halothane induction followed by halothane maintenance. *British Journal of Anaesthesia* 1994; **72**: 554–558.
3. Sorbo S, Hudson RJ, Loomis JC. The pharmacokinetics of thiopental in pediatric surgical patients. *Anesthesiology* 1984; **61**: 666–670.
4. Murat I, Billard V, Vernois J, Zaouter M, Marsol P, Souron R, Farinotti R. Pharmacokinetics of propofol after a single dose in children aged 1–3 years with minor burns. Comparison of three data analysis approaches. *Anesthesiology* 1996; **84**: 526–532.
5. Meistelman C, Saint-Maurice C, Lepaul M, Levron J-C, Loose J-P, Mac Gee K. A comparison of alfentanil pharmacokinetics in children and adults. *Anesthesiology* 1987; **66**: 13–16.
6. Eger EI. Uptake and distribution. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone, 1990; 85–104.
7. Lansdorp D, Vree TB, Janssen TJ, Guelen PJM. Pharmacokinetics of rectal diclofenac and its hydroxy metabolites in man. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 1990; **28**: 298–302.

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Nafamostat mesilate, a kallikrein inhibitor, prevents pain on injection with propofol

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Summary

We have examined the preventative effect of nafamostat mesilate, a kallikrein inhibitor, on pain on injection with propofol in a randomized, double-blind study. A control group (n=110) and a nafamostat (n=103) group received 5% glucose 0.02 ml kg^{-1} and nafamostat 0.02 mg kg^{-1} diluted with 5% glucose, respectively, followed 1 min later by 1% propofol injected at a rate of 200 mg min^{-1}. Pain scores recorded during injection of propofol were significantly less in the nafamostat than in the control group. In another 10 patients, blood concentrations of nafamostat were measured after administration of nafamostat 0.02 mg kg^{-1} i.v. Mean nafamostat concentration 1 min after injection was 0.1 (SD 0.05) μmol litre^{-1}, which is sufficient to inhibit plasma kallikrein activity. We conclude that pretreatment with nafamostat 0.02 mg kg^{-1} significantly reduced pain on propofol injection and this effect may be caused by a reduction in kallikrein activity. (*Br. J. Anaesth.* 1998; **81**: 963–964).

Keywords: pharmacology, nafamostat; anaesthetics i.v., propofol; pain, injection

The mechanism whereby propofol causes pain on i.v. injection is still unclear, although Scott, Saunders and Norman[1] have suggested an effect on an enzymatic cascade, possibly the plasma kallikrein–kinin system. In this cascade, kallikrein converts kininogens to kinins which are chemical mediators of pain. Nafamostat mesilate (Torii Pharmaceutical Co., Tokyo, Japan) is a synthetic serine protease inhibitor used clinically in Japan which inhibits kallikrein activity.[2 3] If propofol-induced pain is attributed to kinins, this drug should decrease the pain via an inhibitory effect on kallikrein activity. This study was designed to test this hypothesis.

Methods and results

This study was approved by the Institutional Committee and all patients (ASA I–II) gave informed consent. In this randomized, double-blind study, 213 adult patients undergoing elective surgery were allocated to control (n=110) and nafamostat (n=103) groups. Patients were premedicated with atropine 0.008 mg kg^{-1} i.m. and butorphanol 1 mg, 30 min before entering the operating room where a 20-gauge intravenous catheter was inserted in the forearm. A 10-mg vial of nafamostat was diluted with 10 ml of 5% glucose, and this solution was stored at 4°C and used within 72 h. One minute after injection of 5% glucose 0.02 ml kg^{-1} (control group) or nafamostat 0.02 mg kg^{-1} (nafamostat group), 1% propofol at room temperature was administered at a rate of 200 mg min^{-1}. During induction, patients were repeatedly asked to report and grade any discomfort or pain as: none=0; only discomfort=1; mild pain=2; moderate pain=3; and severe pain=4. Data are presented as mean (SD) or number of patients.

The groups were similar in age (mean 48 (range 19–78) *vs* 49 (18–83) yr), weight (mean 57 (SD 9) *vs* 58 (10) kg), height (158 (9) *vs* 158 (9) cm), male/female ratio (38/72 *vs* 36/67) and ASA I/II ratio (80/30 *vs* 67/36). The injected doses of propofol in the control and nafamostat groups were 83 (17) and 87 (22) mg (P>0.05, unpaired t test). Pain scores recorded during propofol injection are shown in table 1. The nafamostat group had a significantly lower incidence of propofol-induced pain (P<0.01, Mann–Whitney U test).

Another 10 adult patients undergoing major surgery and requiring monitoring of arterial pressure during anaesthesia were studied. Mean age, weight, height, male/female and ASA I/II ratios were 61 (range 39–76) yr, 59 (SD 14) kg, 157 (8) cm, 6/4 and 4/6. Before induction of anaesthesia, a 22-gauge arterial catheter was inserted into the radial artery. Subsequently, nafamostat 0.02 mg kg^{-1} diluted with 5% glucose was administered i.v., and arterial blood was collected from the catheter. Nafamostat concentrations in blood 1 and 5 min after injection were assayed using high pressure liquid chromatography. Activated coagulation time (ACT) and plasma potassium concentration were measured before, and 1, 5 and 10 min after injection. ACT was measured using ACTester (Quest Medical Inc., TX, USA). Nafamostat concentrations 1 and 5 min after injection were 100 (50) and 16 (7) nmol litre^{-1}. ACT was 110.6 (10.5) s before injection, and 114.3 (9.5), 112.7 (8.6) and 116.3 (8.3) s, 1, 5 and 10 min after injection. Potassium concentrations were 3.803 (0.390) mmol litre^{-1} before injection, and 3.868 (0.456), 3.809 (0.373) and 3.792 (0.364) mmol litre^{-1}, 1, 5 and 10 min after injection. There were no significant changes

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Table 1 Pain scores during injection of propofol (number of patients (%)). Pain scores are: 0=no feeling, 1=only discomfort, 2=mild pain, 3=moderate pain and 4= severe pain. $P<0.01$ between groups

	Pain score				
Group	0	1	2	3	4
Control (n=110)	26 (24%)	10 (9%)	29 (26%)	21 (19%)	24 (22%)
Nafamostat (n=103)	56 (54%)	23 (22%)	17 (17%)	7 (7%)	0 (0%)

in ACT and potassium measurements ($P>0.05$, repeated measures one-way analysis of variance).

Comment

According to the inhibitory effect of nafamostat on kallikrein, 50% inhibition is obtained at concentrations of 1–100 nmol litre^{-1}.[2-4] As this drug is hydrolysed rapidly by blood esterase,[2] its biological half-life is approximately 8 min.[5] We speculated that the i.v. dose of nafamostat to transiently inhibit kallikrein activity would be approximately 1.0 mg. We have demonstrated in our randomized, double-blind study, that nafamostat 0.02 mg kg^{-1} had a significant effect on propofol-induced pain.

We subsequently examined blood concentrations of nafamostat, and also ACT and plasma potassium concentrations after administration of nafamostat 0.02 mg kg^{-1}. Arterial nafamostat concentrations were within the range necessary to inhibit the activity of plasma kallikrein.

Nafamostat is used clinically as an antithrombotic agent but at the dose used in our study, there was no change in ACT. This is consistent with a previous report.[3] The most harmful adverse effect of nafamostat is hyperkalaemia, although this complication appears in only 4.53% of patients with DIC receiving a continuous infusion of nafamostat (data on nafamostat mesilate, 1996, Torii Pharmaceutical Co., Tokyo, Japan). The mechanism of hyperkalaemia is by reduced urinary excretion of potassium, and it has been suggested that intermittent administration may prevent this effect.[5 6] We found no change in potassium concentration using a bolus dose of nafamostat 0.02 mg kg^{-1}.

In summary, pretreatment with nafamostat 0.02 mg kg^{-1}, 1 min before propofol injection significantly inhibited pain on injection. Blood concentrations of nafamostat indicated values sufficient to inhibit plasma kallikrein activity, suggesting kinin generation as a cause of pain.

References

1. Scott RPF, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; **43**: 492–494.
2. Fujii S, Hitomi Y. New synthetic inhibitors of C1r, C1 esterase, thrombin, plasmin, kallikrein and trypsin. *Biochimica et Biophysica Acta* 1981; **661**: 342–345.
3. Hitomi Y, Ikari N, Fujii S. Inhibitory effect of a new synthetic protease inhibitor (FUT-175) on the coagulation system. *Haemostasis* 1985; **15**: 164–168.
4. Pâque EC, Romisch J. Comparative study on the in vitro effectiveness of antithrombotic agents. *Thrombosis Research* 1991; **64**: 11–21.
5. Okajima K, Uchiba M, Murakami K. Nafamostat mesilate. *Cardiovascular Drug Reviews* 1995; **13**: 51–65.
6. Muto S, Imai M, Asano Y. Effects of nafamostat mesilate on Na$^+$ and K$^+$ transport properties in the rabbit cortical collecting duct. *British Journal of Pharmacology* 1993; **109**: 673–678.

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Changes in ionized calcium concentrations and acid–base status during abdominal aortic vascular surgery

S. Jankowski, J. Knighton, R. Dunnill and D. Dickson

Summary

Abdominal aortic surgery may produce significant haemodynamic instability (from a combination of factors: hypovolaemia, acid–base disturbances, vasoactive metabolite release from ischaemic tissues and hypocalcaemia). Calcium is often given after aortic unclamping to attenuate this instability. We studied 20 patients undergoing elective abdominal aortic surgery and observed a triphasic change in ionized calcium concentrations and acid–base status. Initially, during the cross-clamp period (when patients were cardiovascularly stable), ionized calcium concentrations decreased significantly (mean 1.06 (SD 0.08) to 0.91 (0.13) mmol litre^{-1}; $P<0.01$), while a significant metabolic acidosis developed (pH 7.38 (0.05) to 7.30 (0.05); $P<0.05$). Second, release of the aortic cross-clamp resulted in further acidosis (pH 7.27 (0.05) ($P<0.05$) mixed respiratory and metabolic) with a decrease in mean arterial pressure, with no change in ionized calcium concentrations. The third phase was associated with spontaneous restoration of acid–base status and ionized calcium concentrations to normal over 2 h. There was no correlation between units of blood given, volume of blood lost, fluid volume given or duration of aortic cross-clamping and degree of ionized hypocalcaemia. We conclude that ionized hypocalcaemia occurred during the cross-clamp period of aortic surgery, was unrelated to the volume of blood given and did not appear to be responsible for the changes in arterial pressure during surgery. (*Br. J. Anaesth.* 1998; **81**: 965–967).

Keywords: ions, calcium; surgery, vascular; acid–base equilibrium, metabolic acidosis.

Unclamping of the abdominal aorta during vascular surgery may produce cardiovascular instability (arterial hypotension, tachycardia and changes in cardiac output).[1] Several factors may contribute: sudden reduction in left ventricular afterload, blood loss, reactive hyperaemia, metabolic effects, lactic acidosis, hyperkalaemia, hypercapnia and release of toxic, vasoactive products of anaerobic metabolism.[2]

Aggressive fluid management, volume loading before aortic unclamping, sodium bicarbonate or calcium (particularly with large blood transfusions)[1,2] are used to minimize these changes. The role of exogenously administered calcium in maintaining cardiovascular function is unclear and disputed.[3] Further, the practice of giving calcium during blood transfusions is empirical and the rationale for its use dates back to the period when whole blood was given rather than the current practice of giving specific blood products.[4]

In this study we have investigated the changes in ionized calcium concentrations $[Ca^{2+}]$ (physiologically active fraction of blood calcium) and acid–base status during abdominal aortic surgery.

Methods and results

After obtaining approval for the study from the local Ethics Committee and verbal consent, we studied 20 patients (16 males, ASA II or III, mean age 72 (range 51–89) yr), undergoing elective abdominal aortic surgery. All patients were anaesthetized by one of two anaesthetists (R.P.H.D./D.M.D.) using a standard anaesthetic technique. Surgery was performed by the same two surgeons.

All patients were given oral temazepam and metoclopramide as premedication. Before operation a large bore i.v. cannula and radial arterial catheter were inserted under local anaesthesia. Arterial oxygen saturation, heart rate and invasive mean arterial pressure (MAP) monitoring was started. A low thoracic–high lumbar (T12–L1) epidural was sited under local anaesthesia. A test dose of 0.5% bupivacaine 3 ml was given, followed by a loading dose of 8–10 ml of 0.125% bupivacaine with fentanyl 50 μg and an infusion of 0.125% bupivacaine with fentanyl 4 μg ml^{-1} at 10–15 ml h^{-1}. General anaesthesia was induced in all patients with fentanyl 5 μg kg^{-1} and thiopental 3–5 mg kg^{-1}. Vecuronium or pancuronium was used to facilitate tracheal intubation. Anaesthesia was maintained with 1–1.5% isoflurane and 60% nitrous oxide in oxygen. A triple-lumen central venous catheter was then inserted into the right internal jugular vein.

All patients received 10% mannitol 500 ml before clamping of the aorta, glyceryl trinitrate 3–5 mg min^{-1} and dopexamine 3 μg kg^{-1} min^{-1} infusions. Levels of inotropic support were unchanged during aortic cross-clamping. No patient received sodium bicarbonate or calcium. Fluid replacement consisted of crystalloid and colloid infusions (with blood as

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required) to maintain a central venous pressure of at least 12–15 mm Hg.

Blood-gas analysis and ionized [Ca^{2+}] measurements were performed before surgery, before aortic unclamping, at 3, 15 and 30 min after aortic unclamping, and immediately on arrival in the intensive care unit. All blood sample were obtained using 1 ml of arterial blood in 50 u. of dry heparin and analysed using an ABL 500 Radiometer blood-gas and ion-selective analyser for ionized [Ca^{2+}], (normal range=1.05–1.25 mmol litre^{-1}).

Changes from baseline values for metabolic and [Ca^{2+}] data were evaluated using analysis of variance for repeated measurements (ANOVA) with Bonferroni correction for multiple comparisons. Statistical significance was defined as $P<0.05$.

We observed a triphasic response in acid–base status and ionized [Ca^{2+}] (fig. 1). The first phase (aorta cross-clamped) was associated with metabolic acidosis and a significant reduction in ionized [Ca^{2+}] (mean 1.06 (SD 0.08) to 0.91 (0.13) mmol litre; $P<0.01$) with no significant changes in MAP. The second phase (aortic cross-clamp release) was associated with a transient decrease in MAP and further increase in acidosis (metabolic and respiratory) (without further significant changes in ionized [Ca^{2+}]). The third phase was associated with spontaneous restoration of acid–base status and ionized [Ca^{2+}] over 2 h.

There was no significant correlation (Pearson product moment) between degree of reduction in ionized [Ca^{2+}] and aortic cross-clamp time ($r=0.309$, $P=0.189$) (mean 43.4 (SD 11.3) (range 20–65) min), blood loss ($r=0.361$, $P=0.129$) (1280 (569) (range 350–2500) ml), fluid volume given (crystalloid and colloid) ($r=0.149$, $P=0.529$) (2090 (584) (range 1000–3500) ml), units of blood transfused ($r=0.397$, $P=0.083$).

Comment

During aortic cross-clamping we observed metabolic acidosis with ionized hypocalcaemia with no change in MAP. Reduction in ionized [Ca^{2+}] was not related to the number of units of blood transfused, measured blood loss, volume of fluid given or cross-clamp time. Patients not given blood still had significant reductions in ionized [Ca^{2+}]. Metabolic acidosis has been reported previously with lactic acidosis[1] while ionized hypocalcaemia (under life-threatening circumstances) has been reported only once.[5]

Hypovolaemic shock leads to ionized hypocalcaemia and is related to duration of shock.[3] The decrease in ionized [Ca^{2+}] in our patients may reflect hypovolaemia or indicate ischaemic tissues. In patients after cardiorespiratory arrest, ionized hypocalcaemia is common and thought to reflect ischaemia within peripheral tissues as a result of intracellular influx of calcium.[3] In aortic surgery, blood flow to the lower limbs may still occur during the cross-clamp period because of well developed collateral circulations,[1] and ionized hypocalcaemia may indicate washout of blood from ischaemic tissues.

On release of the aortic cross-clamp, a reduction in MAP occurred with no significant change in ionized [Ca^{2+}] but with a further acidosis and hypercapnia. Although reported previously, these metabolic abnormalities are not thought to be entirely responsible for haemodynamic instability during this period. During this type of surgery, the importance of avoiding hypovolaemia and tissue hypoperfusion and preventing depression of the cardiovascular system with aggressive volume replacement has been emphasized.[1,2]

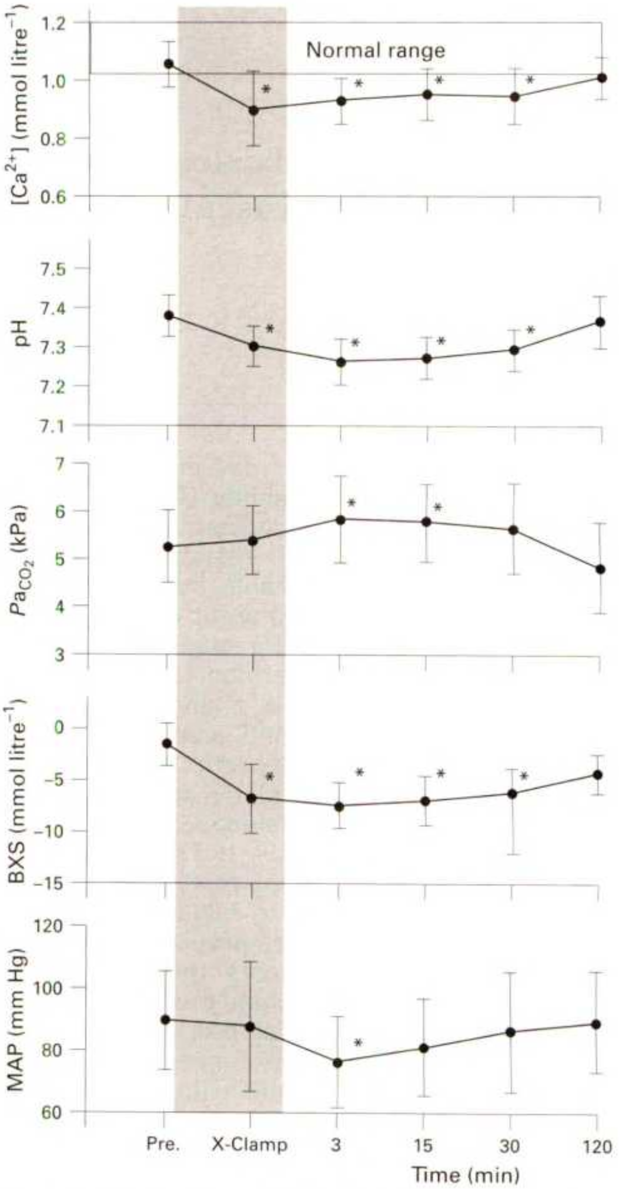

Figure 1 Ionized calcium concentrations [Ca^{2+}], pH, Pa_{CO_2}, base excess (BXS) and mean arterial pressure (MAP) during aortic surgery: pre-aortic clamping (Pre.), during aortic cross-clamping (X-Clamp) and after release of aortic cross-clamp (mean, SD). * $P<0.05$ from baseline.

The role of calcium in the maintenance of cardiovascular function is complicated and depends on many factors (including whether or not a patient is hypo- or normocalcaemic).[3] Previous work suggests that hypocalcaemia (from citrate used as an anticoagulant) may cause haemodynamic instability, but this is disputed because giving calcium may not always restore cardiovascular stability. Hypocalcaemia with blood transfusion is transient and stopping the transfusion results in a spontaneous increase in calcium concentrations.[3] Calcium administration during aortic surgery is empirical and is used to reverse cardiovascular instability (thought to be caused by large (>5 u.) blood transfusions.[6] Rebound hypertension has been documented and indiscriminate use of calcium has resulted in cardiac arrest. Further, it is unclear if giving calcium to patients with ischaemic tissues is detrimental as it may worsen ischaemic injury.[3] Over the next 2 h there was a spontaneous restoration of ionized [Ca^{2+}] and acid–base status with no significant change in MAP. Therefore, giving calcium to patients during aortic surgery may be unnecessary.

In summary, we observed a decrease in ionized [Ca^{2+}] during aortic cross-clamping without change in arterial pressure. The cause of this ionized hypocalcaemia is unclear and probably multifactorial but it may reflect peripheral tissue ischaemia and a degree of hypovolaemia. Blood transfusion did not appear to cause ionized hypocalcaemia. Treatment of ionized hypocalcaemia during abdominal aortic surgery should primarily be volume replacement and calcium given only during severe hypocalcaemia and life-threatening circumstances (preferably while monitoring ionized [Ca^{2+}]). These findings do not relate to emergency aortic surgery.

References

1. Gelman S. The pathophysiology of aortic cross-clamping and unclamping. *Anesthesiology* 1995; **82**: 1026–1060.
2. Brimacombe J, Berry A. A review of anaesthesia for ruptured abdominal aortic aneurysm with special emphasis on preclamping fluid resuscitation. *Anaesthesia and Intensive Care* 1993; **21**: 311–323.
3. Jankowski S, Vincent JL. Calcium administration in the critically ill. When is it indicated? *Journal of Intensive Care Medicine* 1995; **10**: 41–50.
4. Hallowell Churchill W. Transfusion reactions. In: Hallowell Churchill W, Kurtz SR, eds. *Transfusion Medicine*. Oxford: Blackwell Scientific, 1988; 91–106.
5. Prielipp RC, Zaloga GP. Life-threatening hypocalcaemia after abdominal aortic aneurysm repair in patients with renal insufficiency. *Anesthesia and Analgesia* 1991; 73: 638–641.
6. Tomlin PJ. Anaesthesia for elective surgery. In: Tomlin PJ. *Anaesthesia for Vascular Surgery*. London: Wright, 1988; 118–119.

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Vascular properties of isoflurane: comparison between normal and cirrhotic rats

P. KIRSTETTER, F. LAGNEAU, F. LE CORRE, S. CAILMAIL, R. MOREAU, D. LEBREC AND J. MARTY

Summary

Isoflurane is known to dilate blood vessels and to modulate nitric oxide production. Because cirrhosis is characterized by over production of endothelial nitric oxide, isoflurane-induced vasodilatation may be altered in this situation. We have compared the vasodilator effects of isoflurane in normal rats and rats with secondary biliary cirrhosis. Aortic rings (intact or endothelium denuded) from normal and cirrhotic rats were suspended in HEPES solution and preconstricted with KCl 40 mmol litre^{-1}. Isoflurane dose-dependently relaxed vessels in both groups. Maximal relaxation was comparable between normal and cirrhotic rats in intact (mean 80 (SEM 4) *vs* 81 (6)%; ns) and in denuded (100 (4) *vs* 95 (5)%; ns) vessels. Intact vessels relaxed more than denuded vessels in both groups (100 (4) *vs* 80 (4)% (*P*=0.0008) in normal rats and 95 (5) *vs* 80 (6)% (*P*=0.0008) in cirrhotic rats). We conclude that cirrhosis did not modify isoflurane-induced vasodilatation and that the modulator effect of endothelium was conserved. (*Br. J. Anaesth.* 1998; **81**: 968–969).

Keywords: anaesthetics volatile, isoflurane; blood, vessels; liver, cirrhosis; rat

Cirrhosis is characterized by systemic and splanchnic vasodilatation[1] involving over production of nitric oxide by the endothelium.[2] Isoflurane is a volatile anaesthetic known to induce vasodilatation and to modulate endothelium-derived nitric oxide production.[3] Therefore, the pharmacological properties of isoflurane may be modified in cirrhosis. The aim of this study was to compare the response to increasing concentrations of isoflurane in normal rats and in rats with secondary biliary cirrhosis.

Methods and results

The study was approved by the French Agriculture Office, in accordance with European legislation involving animals. We studied male Sprague–Dawley rats (weighing 300–350 g) (Iffa-Credo, France).

Induction of secondary biliary cirrhosis was performed as described previously.[4] Briefly, under ether anaesthesia, the common bile duct was exposed by median laparotomy and occluded by a double ligature with non-resorbable suture (7–0 silk, Peters Laboratories, Bobigny, France). The common bile duct was resected between the two ligatures. A control group using the same weight sham-operated rats was studied in parallel. Animals were studied 4 weeks after operation.

For the preparation of aortic rings, animals were anaesthetized with pentobarbital 50 mg kg^{-1} i.p. The thoracic aorta was removed and placed in a modified HEPES buffer (37°C) aerated with a mixture of 95% oxygen and 5% carbon dioxide. Aortae were dissected clean of fat and extraneous tissues and divided in 3.5–4.0-mm ring segments. In some rings, endothelium was removed mechanically by gently rubbing the intimal surface with a stainless steel rod. The rings were suspended between two L-shaped stainless steel hooks and placed in a 10-ml water-jacketed organ chamber containing a solution composed of (mmol litre^{-1}): NaCl 118.2, KCl 4.7, $NaHCO_3$ 25.0, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 2.5, glucose 11.1 and HEPES 5. Organ chambers were aerated continuously with 95% oxygen and 5% carbon dioxide with pH maintained at 7.35–7.40. Temperature was maintained constant at 37°C. Isometric tension was measured (g) using a force displacement transducer (UF1 Pioden Controls, Paris, France) connected to the upper hook. Tension was recorded on a Servo trace recorder (Sefram, Paris). During the equilibration period of 60 min, the buffer was changed every 15 min and resting tension was adjusted periodically to 1.5 g. Active contraction was induced with KCl 40 mmol litre^{-1} and the integrity of the endothelium was assessed by testing relaxation produced by addition of acetylcholine 10^{-6} mol litre^{-1}.

Endothelium was considered intact when acetylcholine elicited a minimum of 30% vasodilatation. Endothelium was considered removed when acetylcholine induced no vasodilatation. After acetylcholine testing, the rings were washed and re-equilibrated to baseline tension for 60 min. After this new equilibration period, concentration–responses curves were constructed with norepinephrine (noradrenaline), acetylcholine and isoflurane.

Increasing cumulative doses of norepinephrine 10^{-8}–10^{-5} mol litre^{-1} were administrated in rings from control (n=12) and cirrhotic (n=12) rats. The same

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procedure was performed in rings without endothelium from control (n=12) and cirrhotic (n=12) rats.

Rings were preconstricted with norepinephrine 10^{-5} mol litre^{-1} (maximal contraction). When a plateau of maximal contraction was reached, increasing cumulative doses of acetylcholine 10^{-8}–10^{-5} mol litre^{-1} were then administrated in rings from control (n = 6) and cirrhotic (n=6) rats.

Aortic rings were preconstricted (KCl 40 mmol litre^{-1}) and exposed to cumulative concentrations of isoflurane (1–5%). Isoflurane was delivered using a calibrated agent-specific vaporizer (Abott, France). Aeration concentrations of isoflurane were monitored and adjusted using an anaesthetic agent monitor. Each concentration was maintained until the effect on the aortic ring reached a plateau (i.e. an average of 10 min). Isoflurane was administered to intact rings from normal (n=12) and cirrhotic (n=8) rats. Isoflurane was also administered in denuded rings from normal (n=12) and cirrhotic (n=6) rats.

Data are expressed as mean (SEM). Contractions to norepinephrine are expressed in grams. Relaxation to acetylcholine and isoflurane is expressed as percentage of precontraction obtained with norepinephrine 10^{-5} mol litre^{-1} or KCl 40 mmol litre^{-1}. Data were analysed statistically using ANOVA. The statistical package was Statview SE (Abacus Concept, Inc, Berkley, USA, CA). Differences were considered significant at P<0.05.

In intact rings, the maximal response to norepinephrine was significantly lower in rings from cirrhotic rats compared with controls (1.95 (0.18) *vs* 2.91 (0.42) g; P=0.0007). In contrast, contraction to norepinephrine was comparable between denuded rings from cirrhotic and control rats (1.48 (0.24) *vs* 1.29 (0.15) g; P=0.49). Acetylcholine-induced relaxation was significantly greater in cirrhotic than in control rats (47.5 (5.6) *vs* 22.6 (2.8)%; P=0.003).

After isoflurane, maximal relaxation was comparable between normal and cirrhotic rats in intact (80 (4) *vs* 81 (6)%; ns) and denuded (100 (4) *vs* 95 (5)%; ns) vessels. In contrast, intact vessels relaxed more than denuded vessels in both groups of rats (100 (4) *vs* 80 (4)% (P=0.0008) in normal rats and 95 (5) *vs* 80 (6)% in cirrhotic rats) (fig. 1).

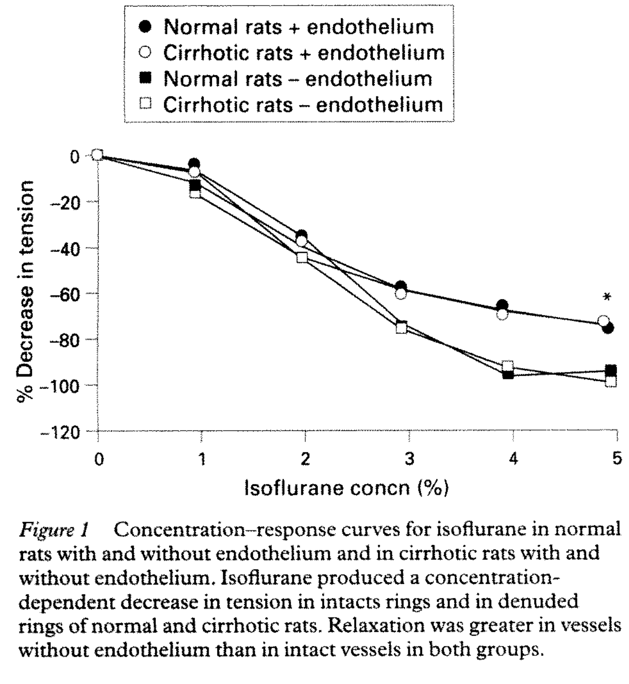

Figure 1 Concentration–response curves for isoflurane in normal rats with and without endothelium and in cirrhotic rats with and without endothelium. Isoflurane produced a concentration-dependent decrease in tension in intacts rings and in denuded rings of normal and cirrhotic rats. Relaxation was greater in vessels without endothelium than in intact vessels in both groups.

Comment

We have confirmed that vascular reactivity to an a agonist, norepinephrine, was decreased in isolated vessels from cirrhotic rats compared with controls.[5] Among the hypotheses to explain this result, over production of nitric oxide by the endothelium of vessels from cirrhotic animals has been proposed.[2]

In normal rats, it has been shown previously that isoflurane-induced vasodilatation was more important in vessels without endothelium than in intact vessels.[3] To explain this result, we hypothesized that isoflurane inhibits nitric oxide production and at the same time dilates vessels, leading to relative constriction in vessels with endothelium.[6] In our study, this result was also observed in rats with cirrhosis. As a result, modulation of isoflurane-induced vasodilatation by endothelium[3] was conserved in vessels of cirrhotic rats in which over production of nitric oxide took place in the endothelium.

As endothelial production of nitric oxide is increased in cirrhosis and as isoflurane modulates this production, the effect of isoflurane in intact vessels of cirrhotic rats should be different from the effect observed in intact vessels from controls. In fact, we showed that isoflurane-induced vasodilatation was comparable between normal and cirrhotic rats, suggesting that endothelial over production of nitric oxide did not alter vascular reactivity to isoflurane. This result strongly suggests that vasodilatation produced by isoflurane is independent of nitric oxide.

In summary, we conclude that isoflurane-induced vasodilatation was not modified by cirrhosis, a condition involving over production of nitric oxide by the endothelium, and that the modulator effect of endothelium was conserved.

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References

1. Gaudin C, Braillon A, Poo JL, Moreau R, Hadengue A, Lebrec D. Regional sympathetic activity, severity of liver disease and haemodynamics in patients with cirrhosis. *Journal of Hepatology* 1991; **13**: 161–168.
2. Martin PY, XU DL, Niederberger M, Weigert A, Tsai P, St John J, Gines P, Schrier RW. Upregulation of endothelial constitutive NOS: a major role in the increased NO production in cirrhotic rats. *American Journal of Physiology* 1996; **270**: F494–F499.
3. Kirstetter P, Lagneau F, Lucas O, Krupa Y, Marty J. Role of endothelium in the modulation of isoflurane-induced vasorelaxation in rat thoracic aorta. *British Journal of Anaesthesia* 1997; **79**: 84–87.
4. Kirstetter P, Moreau R, Soupison T, Cailmail S, Lebrec D. Role of the sympathetic cardiovascular tone in the control of arterial pressure in rats with cirrhosis. *Liver* 1996; **16**: 263–266.
5. Castro A, Jimenez W, Claria J, Ros J, Martinez JM, Bosch M, Arroyo V, Piulats J, Rivera F, Rodés J. Impaired responsiveness to angiotensin II in experimental cirrhosis: role of nitric oxide. *Hepatology* 1993; **18**: 367–372.

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Sedation depends on the level of sensory block induced by spinal anaesthesia

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Summary

We have investigated the relationship between the extent of spinal block and occurrence of sedation. In a first series of 43 patients, the distribution of sedation score (measured on the Ramsey scale) was related to the extent of spinal block (pinprick). In a second series of 33 patients, the relationship between sedation score and spinal block persisted after injection of midazolam 1 mg. This study confirmed that high spinal block was associated with increased sedation. (*Br. J. Anaesth.* 1998; **81**: 970–971).

Keywords: anaesthetic techniques, subarachnoid; hypnotics benzodiazepine, midazolam; sedation

It is stated frequently that patients with spinal block may be drowsy, although they may not have received any sedative drugs.[1] It has been demonstrated also that high spinal anaesthesia increases sensitivity to the sedative effect of midazolam,[2-4] suggesting that spinal or epidural block has a sedative action. Therefore, we have conducted a study to investigate the effect of spinal block on patient awareness and to relate this effect to extent of block.

Methods and results

Initially, we studied 43 unpremedicated patients undergoing general surgery under spinal anaesthesia (mean age 57 (range 17–91) yr). Hyperbaric 0.5% bupivacaine was used for spinal anaesthesia in the dose range 5–20 mg, according to the surgical procedure requirements of the anaesthetist in charge. The level of sensory block was evaluated by pinprick at 5, 10, 20, 30 and 45 min after administration of bupivacaine. Sedation was estimated at the same time using the Ramsey scale (1=anxious and agitated; 2=co-operative and tranquil; 3=drowsy but responsive to command; 4=asleep but responsive to a glabellar tap; 5=asleep with a sluggish response to tactile stimulation; 6=asleep and no response) by an independent observer unaware of the extent of block.[4] Monitoring included heart rate, arterial pressure and Sa_{O_2}. Hypotension (defined as a decrease in systolic arterial pressure less than 90 mm Hg) was treated by ephedrine 3–12 mg i.v.

We then studied a second group of 33 patients (mean age 58 (range 25–83) yr) also undergoing surgery under spinal anaesthesia using 0.5% hyperbaric bupivacaine in the same dose range. After completion of spinal block, these patients were given an i.v. bolus of midazolam 1 mg. Sedation scores were determined before and 5, 10, 20, 30 and 45 min after administration of midazolam. Patients in this group were monitored as before.

In both groups we examined the relationship between maximum sedation score and maximum extent of sensory block and age. Data were analysed using a contingency table. $P<0.05$ was considered significant.

The maximum upper levels of sensory block were T2 and L3. A significant relationship was found between the maximum extent of sensory block and level of sedation in the first series of patients (fig. 1A) ($P<0.03$) and in the second series after administration of midazolam (fig. 1B) ($P<0.05$). Three patients in the first group and one in the second group experienced hypotension without worsening of sedation score. There were no episodes of oxygen desaturation. There was no relationship between age and extent of block.

Comment

Although sedation scores were not distributed in the complete range of the Ramsey scale, we have shown an association between the level of sensory block and degree of sedation. There was no association with age. I.v. administration of midazolam increased sedation scores but did not change the relationship between the extent of sensory block and degree of sedation. In agreement with previous studies,[2-4] and with daily clinical practice, we found that, especially when the block extended to the upper thoracic segments, after a small dose of midazolam (1 mg), some patients (27%) were unresponsive to verbal stimulation and only reacted to a light glabellar tap.

High spinal block may impair awareness because of hypotension or arterial oxygen desaturation. There were no such events in our study. A direct effect of local anaesthetic on the brainstem may explain sedation. Thus to avoid significant plasma absorption of local anaesthetic, we studied spinal instead of epidural anaesthesia. Nevertheless, Inagaki and colleagues have demonstrated that i.v. lidocaine did not produce sedation while epidural lidocaine did,[6] suggesting that the sedative effect was more likely to be caused by the anaesthetic block rather than the

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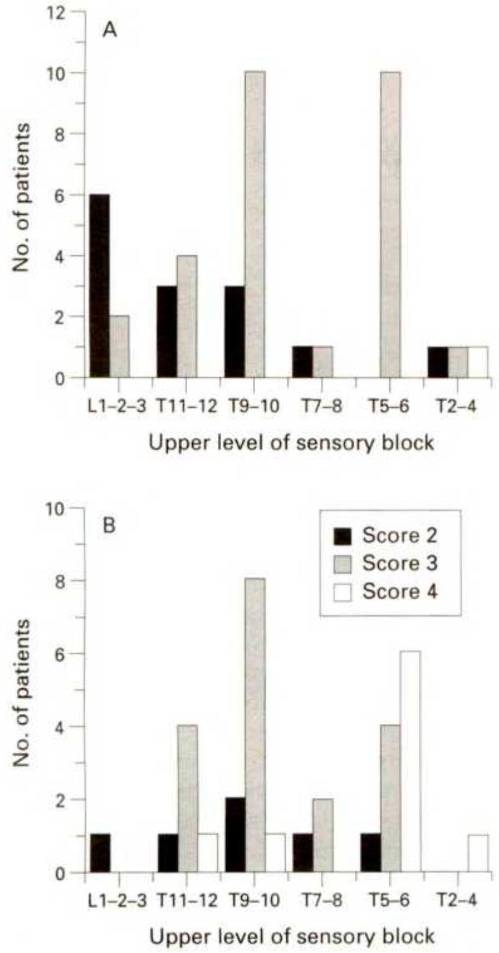

Figure 1 A: Sedation scores according to the level of sensory block (n=43). B: Sedation scores after administration of midazolam according to the level of sensory block (n=33).

effect of the local anaesthetic on the central nervous system.

Spinal block results in loss of proprioceptive inputs from muscles and joints which are thought to contribute to maintenance of awareness. Inagaki and colleagues also suggested that a decrease in nociceptive stimulation was implicated in the increased sensitivity to anaesthetic agents.[6] The lack of warm and cold sensations could also be partly implicated.

In summary, we have shown that high spinal block was associated with sedation. This confirms that sedation must be carefully titrated in patients with high central block.

References

1. Greene NM. *Physiology of Spinal Anesthesia*, 3rd Edn. Baltimore: Williams and Wilkins, 1981; 45–54.
2. Ben-David B, Vaida S, Gaitini L. The influence of high spinal anesthesia on sensitivity to midazolam sedation. *Anesthesia and Analgesia* 1995; **81**: 525–528.
3. Tverskoy M, Shagal M, Finger J, Kissin I. Subarachnoid bupivacaine blockade decreases midazolam and thiopental hypnotic requirements. *Journal of Clinical Anesthesia* 1994; **6**: 487–490.
4. Tverskoy M, Shifrin V, Finger J, Fleyshman G, Kissin I. Effect of epidural bupivacaine block on midazolam hypnotic requirements. *Regional Anesthesia* 1996; **21**: 209–213.
5. Ramsey MAE, Savage TM, Simpson BRJ, Goodwin R. Controlled sedation with alfaxolone–alphadolone. *British Medical Journal* 1974; **2**: 656–659.
6. Inagaki Y, Mashimo T, Kuzukawa A, Tsuda Y, Yoshiya I. Epidural lidocaine delays arousal from isoflurane anesthesia. *Anesthesia and Analgesia* 1994; **79**: 368–372.

British Journal of Anaesthesia 1998; **81**: 972–973

Topical anaesthesia of intact skin: liposome-encapsulated tetracaine *vs* EMLA

R. FISHER, O. HUNG, M. MEZEI AND R. STEWART

Summary

In this randomized, double-blind study, we have compared the ability of 5% liposome-encapsulated tetracaine (amethocaine) (LET) *vs* 5% eutectic mixture of local anaesthetics (EMLA) to produce local anaesthesia of intact skin in 40 healthy volunteers. Volunteers had both preparations applied to their forearms under an occlusive dressing for 1 h. Superficial anaesthesia was measured by a total of nine 1-mm pinpricks on each arm. Deeper anaesthesia was assessed by single insertion of a sterile 22-gauge needle to a depth of 3 mm and pain was reported on a visual analogue scale (VAS). If the volunteer perceived greater than four of the 1-mm pinpricks, the 3-mm insertion was not performed. Results showed that the number of pinpricks perceived was significantly less ($P<0.01$) for LET (median 1.0; range 0–9) *vs* EMLA (1.5; 0–9). In volunteers who had deeper anaesthesia assessed, there was no significant difference ($P=0.065$) in VAS scores for LET (mean 1.5 (SD 1.4); $n=34$) *vs* EMLA (2.4 (2.1); $n=28$). Overall anaesthetic effect, as ranked by all of the subjects, was significantly better for LET compared with EMLA ($P=0.024$). We have demonstrated that when applied in equal volumes, 5% LET produced better superficial local anaesthesia than EMLA. (*Br. J. Anaesth.* 1998; **81**: 972–973).

Keywords: anaesthetics local, EMLA; anaesthetics local, tetracaine

Currently, many hospitals use topical anaesthetic cream to help alleviate pain and decrease the stress of venepuncture in paediatric patients. One of the most widely used topical anaesthetics for intact skin is a 5% eutectic mixture of local anaesthetics (EMLA: 2.5% lidocaine and 2.5% prilocaine). EMLA produces good dermal anaesthesia after the recommended 1-h application.[1]

Investigation of dermal penetration of several local anaesthetics has shown that tetracaine (amethocaine) is the most effective drug for percutaneous local anaesthesia.[2] Coating of drugs with phospholipids, a process known as "liposome-encapsulation", represents an innovative method of drug delivery for local anaesthetics. It has been established that liposome-encapsulation increases both the rate of penetration and effective concentration in the epidermis of topically applied drugs.[3] Based on this, we believed that liposome-encapsulated tetracaine (LET) would be an effective topical anaesthetic.

Methods and results

In this randomized, double-blind study, we have compared the efficacy of 5% LET with 5% EMLA for providing superficial and deep anaesthesia in 40 healthy volunteers. The study was approved by the Research Review Committee of the Victoria General Hospital, Dalhousie University, Halifax, NS, Canada. LET was prepared at the College of Pharmacy, Dalhousie University, Halifax, NS, Canada, based on a well-established and patented method.[4] EMLA was obtained from Astra Pharmaceuticals Products Inc. (Westborough, MA, USA). The colour and consistency of the LET cream was adjusted to appear identical to that of EMLA.

After obtaining written informed consent, the surface of both forearms was swabbed with 70% isopropyl alcohol solution to remove excess skin oils. Then, 1 ml of either 5% LET or 5% EMLA was applied randomly (tossing of a coin) to a 4x4 cm area on each arm. These areas were covered with an occlusive dressing (Tegaderm, 3M, London, Ontario, Canada). After 1 h, the occlusive dressings were removed and the creams wiped off in the same order in which they had been applied. All subjects were scored immediately for the presence of erythema or blanching at the application site.

Both arms were tested for degree of superficial and deep anaesthesia. Superficial anaesthesia was assessed using a sterile 20-gauge needle (Becton Dickinson, Franklin Lanes, NJ, USA) inserted via a small cork so that the needle protruded 2 mm. Subjects were pricked a total of nine times over a 3 × 3 cm grid superimposed over the application site. An initial pinprick in a non-anaesthetized portion of the forearm was used for comparison. Results were recorded as the number of painful stimuli out of nine.

The study design stipulated that if a subject felt greater than four of the nine pinpricks, deeper anaesthesia would not be tested in that arm. If the subject felt four or less of the nine pinpricks, a 22-gauge needle was inserted randomly in the area of application to a depth of 3 mm and the subject's response was recorded on a 0–10 visual analogue scale (VAS).

Finally, we asked subjects to rate their impression of both creams in terms of overall anaesthetic effect.

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Responses were recorded as no effect, some effect or good effect. Subjects were also asked to state which cream they preferred. Responses were recorded as "no difference", "prefer A" or "prefer B".

Superficial pinprick data were compared using McNemar's test. VAS scores were compared using a Wilcoxon non-parametric test. Chi-square analysis was used to compare the number of sites tested for deeper anaesthesia for LET *vs* EMLA. Overall anaesthetic effect was compared using a Wilcoxon signed rank test. The assigned rankings were: 0=no effect, 1=some effect, 2=good effect, 3=best effect. Data are expressed as mean (SD). $P<0.05$ was considered significant.

We studied 40 volunteers (26 females) aged 22–64 yr (mean 34.7 yr). Mean application time was 60.9 (1.0) min for both preparations. In the assessment of superficial anaesthesia, the number of pinpricks perceived was significantly less ($P<0.01$) for LET (median 1.0; range 0–9) compared with EMLA (1.5; 0–9). Significantly fewer ($P<0.01$) of the volunteers in the LET ($n=6$) group felt greater than four of the nine superficial pinpricks compared with the EMLA group ($n=12$). Assessment of deeper anaesthesia demonstrated a trend towards lower VAS scores for LET (1.5 (1.4); $n=34$) *vs* EMLA (2.4 (2.1); $n=28$), but this difference was not statistically significant ($P=0.065$).

Overall anaesthetic effect was significantly better for LET than for EMLA ($P=0.024$). Twenty-four (62.5%) volunteers preferred LET while nine (20%) preferred EMLA. Both preparations were judged to have good anaesthetic effects in all 33 of the volunteers. Certain individuals may require an extended period of application in order to achieve adequate local anaesthesia.

Side effects included mild erythema in 32 (80%) LET subjects. EMLA produced blanching in 23 (58%) subjects. The occlusive dressing produced mild localized itching in the area of skin contact in two volunteers.

Comment

We have demonstrated that 5% LET produced better superficial local anaesthesia than EMLA. This finding was likely the result of increased absorption of the liposomal preparation through the stratum corneum.[3] In the assessment of deeper anaesthetic effect, there was a trend towards lower VAS scores for the LET group compared with the EMLA group, but this difference was not statistically significant. Testing a larger number of subjects or testing all volunteers regardless of superficial anaesthesia may have revealed a significant difference between the two preparations.

In the assessment of overall anaesthetic effect, the majority of subjects preferred LET (62.5%). However, it is interesting that 20% preferred EMLA while 12.5% found no difference; 5% had no anaesthesia with either preparation. These differences are probably related to individual differences in skin composition and thickness which alter the absorption of both preparations.

Erythema seen with LET is probably secondary to the vasodilating action of tetracaine,[5] as application of empty liposomes to intact skin produces no erythema.[6] If a local anaesthetic cream is being used before i.v. insertion, vasodilatation would be beneficial. Future studies are planned to compare the efficacy of LET *vs* EMLA to produce local anaesthesia of intact skin before i.v. insertion.

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References

1. Maunuksela E-L, Korpela R. Double-blind evaluation of lignocaine–prilocaine cream (EMLA) in children. Effect on the pain associated with venous cannulation. *British Journal of Anaesthesia* 1986; 58: 1242–1245.
2. McCafferty D, Woolfson AD, Boston V *In vivo* assessment of percutaneous local anaesthetic preparations. *British Journal of Anaesthesia* 1989; 62 17–21.
3. Foldvari M, Gesztes A, Mezei M. Dermal drug delivery by liposomal encapsulation· Clinical and electron microscopic studies. *Journal of Microencapsulation* 1990; 7. 479–489.
4. Mezei M, Gesztes A. Liposomal local anesthetics and analgesics. US Patent No. 4937078, 1990.
5. Willatts DG, Reynolds F. Comparison of the vasoactivity of amide and ester local anaesthetics. *British Journal of Anaesthesia* 1985; 57: 1006–1011.
6. Gesztes A, Mezei M. Topical anaesthesia of skin by liposome-encapsulated tetracaine. *Anesthesia and Analgesia* 1988; 67: 1079–1081.

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Effect of infiltration with ropivacaine on blood loss during reduction mammoplasty

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Summary

Ropivacaine is a new aminoamide local anaesthetic agent. Unlike other agents in its class, such as bupivacaine, it has been found to be vasoconstrictive. We have sought to investigate if this property is clinically useful and may reduce surgical blood loss. Reduction mammoplasty is a procedure in which considerable blood loss may occur. We have compared pre-incision infiltration of ropivacaine 75 mg in 0.9% saline 60 ml with the current practice of infiltration with bupivacaine 75 mg in 0.9% saline 60 ml and epinephrine (adrenaline) 5 μg ml^{-1}. We studied five subjects; each received both solutions by infiltration, one to each breast, in random order and both the operating surgeon and anaesthetist were blind to the solution given. For data analysis, blood loss was expressed in ml/kg of tissue excised. There was no significant difference between the two regimens for duration of surgery or amount of tissue excised; however, ropivacaine was associated with markedly greater intraoperative blood loss than bupivacaine (median 696 (range 305–1366) ml kg^{-1} *vs* 300 (169–608) ml kg^{-1}; P=0.04, Wilcoxon rank sum test). Postoperative blood loss was not significantly different between groups (116 (14–173) ml kg^{-1} *vs* 98 (13–332) ml kg^{-1}; P=0.69, Wilcoxon rank sum test). We conclude that the vasoconstrictive properties of ropivacaine were not sufficiently great to merit its use as a sole agent for infiltration before reduction mammoplasty. (*Br. J. Anaesth.* 1998; **81**: 974–975).

Keywords: anaesthetics local, bupivacaine; anaesthetics local, ropivacaine; anaesthetic techniques, i.v. regional; surgery, plastic

Reduction mammoplasty is a relatively common procedure in which significant blood loss may occur. During the 1970s, blood loss during this type of surgery often required replacement by transfusion.[1] However, significant reduction in blood loss and therefore transfusion requirements occur when epinephrine (adrenaline) is infiltrated before surgical incision.[2] It is now common practice to infiltrate breast tissue with a combination of bupivacaine and epinephrine 1:200 000 before dissection. This provides a combination of perioperative local anaesthesia with vasoconstriction.

Ropivacaine is a newly introduced aminoamide local anaesthetic agent which is closely related structurally to mepivacaine and bupivacaine. However, it is less toxic than bupivacaine which has been associated with adverse cardiac effects after rapid systemic absorption or inadvertent intravascular injection.[3] In addition, after subcutaneous infiltration, ropivacaine has a greater duration of action than bupivacaine which has been attributed to the intrinsic vasoconstrictor properties of the drug.[3]

The aim of this study was to investigate if ropivacaine alone, in comparison with a bupivacaine–epinephrine mixture (our current standard regimen), provided any useful vasoconstriction during reduction mammoplasty.

Method and results

After obtaining local Ethics Committee approval and written informed consent, we recruited five patients in a pilot study. Subjects were female, ASA I–II, aged 27–32 yr and undergoing elective reduction mammoplasty. Exclusion criteria included gross breast asymmetry and known sensitivity to local anaesthetic agents.

Patients underwent a standard general anaesthetic without premedication. Anaesthesia was induced with propofol and maintained with isoflurane and 70% nitrous oxide in oxygen. The trachea was intubated and the lungs ventilated to normocapnia after administration of atracurium. Residual neuromuscular block was antagonized with neostigmine and glycopyrrolate. Peri- and postoperative analgesia were supplemented with morphine as required.

The same surgeon operated on all patients. Patients provided their own comparison as each subject received both solutions. The surgeon and anaesthetist were blind to the solution used for infiltration into each breast, which was prepared and provided by an investigator. The solutions were administered to each side (breast) in random order. All drug infiltration was performed by the same surgeon immediately before incision of each breast. The local anaesthetic solutions were: bupivacaine 75 mg in 0.9% saline 60 ml with epinephrine 5 μg ml^{-1}, and ropivacaine 75 mg in 0.9% saline 60 ml without epinephrine.

The skin was incised by scalpel and tissue was dissected using argon-assisted diathermy. Operative blood loss from each breast was measured separately by weighing of swabs and the use of plastic drapes

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Table 1 Amount of breast tissue excised from each side and intra- and postoperative blood loss. Each side was infiltrated before incision with either ropivacaine 75 mg in 0.9% saline 60 ml or bupivacaine 75 mg in 0.9% saline 60 ml with epinephrine 5 μg ml^{-1}

Patient No.	Ropivacaine					Bupivacaine with epinephrine 5 μg ml^{-1}				
	Excised tissue	Intraop. blood loss		Postop. blood loss		Excised tissue	Intraop. blood loss		Postop. blood loss	
	(g)	(ml)	(ml kg^{-1})	(ml)	(ml kg^{-1})	(g)	(ml)	(ml kg^{-1})	(ml)	(ml kg^{-1})
1	432	590	1366	50	116	366	124	338	30	82
2	849	259	305	12	14	603	102	169	200	332
3	366	198	541	7	19	393	118	300	5	13
4	375	352	939	65	173	387	198	512	38	98
5	795	554	696	120	152	745	453	608	115	154

with collection pockets. Postoperative blood loss was measured by surgical wound drains. In addition, the amount of tissue excised and the time from infiltration to completion of each dissection were measured.

Published data suggested that mean blood loss with epinephrine would be approximately 150 ml (SD 90 ml).[2] For a study power of at least 80% we calculated that 20 patients would be required to detect a difference in blood loss of 90 ml. Data were analysed statistically using SPSS for Windows 95–Wilcoxon rank sum test. We did not assume that the data would fit a normal distribution. Level of significance was taken as $P<0.05$.

Data from all subjects are shown in table 1. There was no significant difference between the two regimens for duration of surgery or amount of tissue excised. For analysis, blood loss was expressed in ml/kg of tissue excised. We found that administration of ropivacaine was associated with markedly greater intraoperative blood loss than the bupivacaine–epinephrine mixture (median 696 (range 305–1366) ml kg^{-1} *vs* 300 (169–608) ml kg^{-1}; $P=0.04$, Wilcoxon rank sum test). Postoperative blood loss did not differ significantly between the two solutions (116 (14–173) ml kg^{-1} *vs* 98 (13–332) ml kg^{-1}; $P=0.69$, Wilcoxon rank sum test).

Comment

We have found that ropivacaine was associated with significantly greater blood loss than bupivacaine–epinephrine during reduction mammoplasty. It was our original intention to study 20 patients, but after five patients it was apparent that a large difference may exist and therefore the study was halted and treatment codes were broken. We compared ropivacaine with our current practice of using a mixture of bupivacaine with epinephrine 5 μg ml^{-1}; it would not have been acceptable to compare it with bupivacaine alone as this is known to be associated with extensive blood loss and may have resulted in the need for transfusion or possibly asymmetrical wound healing.[2]

Infiltration of ropivacaine has been shown to result in more prolonged analgesia than plain bupivacaine.[4] We did not examine the quality or duration of postoperative analgesia. In *in vitro* experiments, ropivacaine has been shown to produce vasoconstriction in isolated femoral artery preparations,[5] and *in vivo* studies examining capillary blood flow with a laser Doppler technique have shown a significant reduction in blood flow.[6] In addition, ropivacaine may be less toxic than bupivacaine,[3] suggesting that it may be preferable to bupivacaine as a local anaesthetic for reduction mammoplasty.

There may be some advantage in using a mixture of ropivacaine with epinephrine. This may prove more efficacious in terms of both blood loss and duration of postoperative analgesia; further studies are required.

In summary, we have found that in respect of intraoperative blood loss, ropivacaine was not suitable for use as a sole agent for infiltration before reduction mammoplasty. Further studies are required to examine the optimum dose of epinephrine for use with ropivacaine.

References

1. Yu JC, Noone RB, LaRossa D. Autotransfusion and reduction mammoplasty: a reappraisal in the 1990s *Plastic and Reconstructive Surgery* 1994, 94: 328–332.
2. Brantner JN, Peterson HD. The role of vasoconstrictors in the control of blood loss in reduction mammoplasty *Plastic and Reconstructive Surgery* 1985; 75 339–341.
3. McClure JH. Ropivacaine. *British Journal of Anaesthesia* 1996; 76: 300–307.
4. Cederholm I, Akerman B, Evers H Local analgesic and vascular effects of intradermal ropivacaine and bupivacaine in various concentrations with and without addition of adrenaline in man. *Acta Anaesthesiologica Scandinavica* 1994; 38: 322–327.
5. Nakamura K, Toda H, Kakuyama M, Nishiwada M, Yamamoto M, Hatano Y, Mori K. Direct vascular effect of ropivacaine in femoral artery and vein of the dog *Acta Anaesthesiologica Scandinavica* 1993; 37: 269–273.
6. Kopacz DJ, Carpenter RL, Mackey DC Effect of ropivacaine on cutaneous capillary blood flow in pigs. *Anesthesiology* 1989, 71· 69–74.

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CASE REPORTS

Anaesthetic management of a woman who became paraplegic at 22 weeks' gestation after a spontaneous spinal cord haemorrhage secondary to a presumed arteriovenous malformation

A. J. Eldridge, M. Kipling and J. Watt Smith

Summary

A 19-yr-old woman developed a paraplegia with a T10 sensory level at 22 weeks' gestation. The spinal injury was caused by spontaneous bleed of a presumed arteriovenous malformation in the spinal cord. She presented for Caesarean section at term because of the breech position of her fetus. The successful use of a combined spinal epidural–regional anaesthetic is described and the risks of general and regional anaesthesia are discussed. (*Br. J. Anaesth.* 1998; **81**: 976–978).

Keywords: anaesthesia, obstetric; complications, arteriovenous malformation; pregnancy; anaesthetic techniques, subarachnoid; anaesthetic techniques, epidural

The anaesthetic management of pregnant paraplegic patients has been well documented. However, there is no previous report of the anaesthetic management of a woman requiring a Caesarean section who had become paraplegic during her pregnancy after a subarachnoid bleed in the spinal cord.

Historically, subarachnoid bleeds have been implicated in 5–12% of maternal deaths,[1–3] although more recent estimates suggest a slightly lower incidence.[4 5] However, this mortality is almost entirely caused by intracranial bleeds. Spontaneous subarachnoid haemorrhage can also occur in the spinal canal. While spinal canal bleeds are less likely to be fatal, they may cause devastating neurological sequelae. These bleeds are usually caused by arteriovenous malformations (AVM).

The incidence of spinal canal AVM is 3.4–11.5 % of all spinal tumours.[6 7] They are either epidural or intradural, with intradural lesions being on the surface or in the substance of the cord. The average age at presentation is 57 yr for epidural AVM and 37 yr for spinal cord AVM.[8] AVM are nine times more common in males than females.[8]

AVM have the potential for spontaneous haemorrhage or to cause cord ischaemia. Characteristic symptoms at presentation are leg weakness, sensory deficit and a disturbance of micturition and defecation. Nerve root pain may also occur. When these symptoms are caused by cord ischaemia, onset is usually slowly progressive, sometimes taking more than 1 yr to develop. In contrast, haemorrhage presents with an acute onset of symptoms and is the cause of presentation in approximately 10% of dural AVM[8] and up to 45% of spinal cord AVM.[9]

The presence of a known spinal AVM is generally considered a contraindication to neuroaxial anaesthesia, although Ong and colleagues reported the successful management of a woman with a large asymptomatic cervical AVM who had a Caesarean section performed under spinal anaesthesia.[10]

Case report

A previously healthy 19-yr-old woman in her first pregnancy presented at 22 weeks' gestation with radicular pain in both legs and a urinary tract infection. She was treated with antibiotics and analgesics and discharged. She returned 7 days later with leg weakness and urinary retention. Over the following 12 h she developed a T10 sensory level and near complete flaccid paralysis of her legs. She was referred for a neurosurgical opinion and magnetic resonance imaging, which revealed a bleed in the spinal cord at T10 consistent with a small AVM (fig. 1). Oedema caused mild swelling of the cord from T9 to T12, but no surface abnormality was seen on the cord or in the epidural space.

Surgery was not indicated and the patient was transferred to the regional spinal rehabilitation unit. Over the following weeks she had some recovery of power in her legs and could stand with the aid of a frame. She was eventually discharged home at 32 weeks' gestation.

Her pregnancy was further complicated by the breech position of her fetus and therefore an elective operative delivery was planned. She was seen in our anaesthetic assessment clinic where she expressed a strong preference to be awake for the delivery.

A literature review was undertaken, the MRI scan was discussed and opinions sought from neurologists, neurosurgeons and anaesthetists at two spinal injury centres who advised first that regional anaesthesia was not contraindicated and second that the patient had a small risk of developing autonomic hyperreflexia in the perioperative period.

Women with spinal injuries commonly go into premature labour. Depending on the neurological deficit, the patient may be unaware of labour starting. This patient presented because her urinary catheter fell out. Early labour was diagnosed and a semi-elective Caesarean section performed.

A careful assessment was made of her neurological

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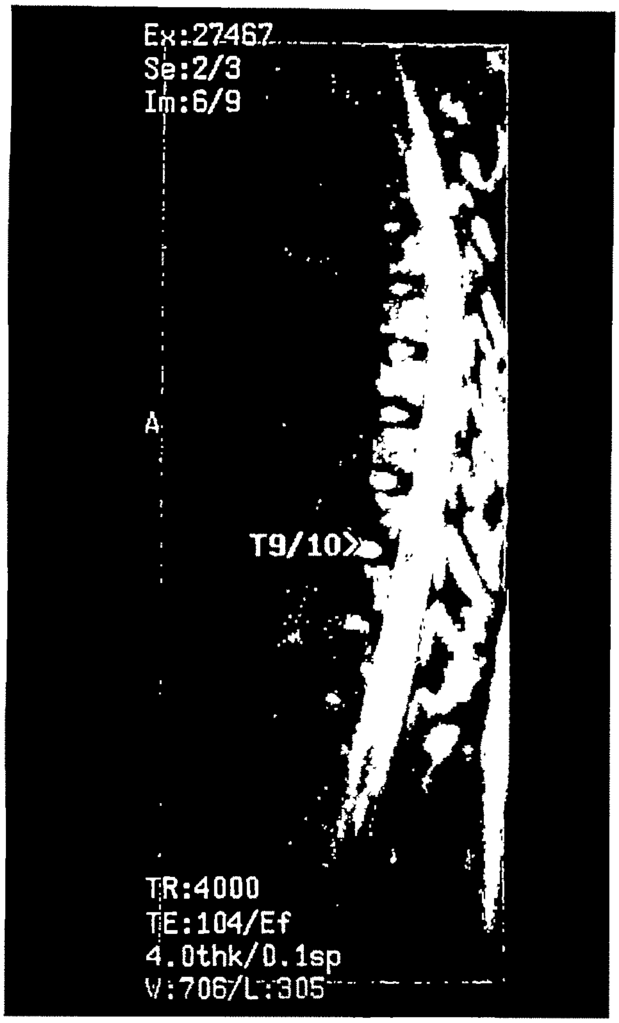

Figure 1 Magnetic resonance image of the thoracic spine with an area of hyperintensity indicated at T9–10. The appearance is consistent with a small haematoma in the cord secondary to an underlying arteriovenous malformation.

deficit before anaesthesia was started. Routine monitoring of ECG, arterial pressure and oxygen saturation was established. If general anaesthesia had been used, we would have inserted intra-arterial pressure monitoring but felt that non-invasive arterial pressure monitoring at 1-min intervals was sufficient for the anticipated slower changes in arterial pressure associated with regional anaesthesia.

We wished to extend the regional block gradually to maintain haemodynamic stability. Additionally, to minimize pressure changes in the epidural space, we wanted to avoid using large volumes of epidural local anaesthetic. We therefore elected to use a combined spinal–epidural technique with a slightly lower dose than usual of intrathecal hyperbaric bupivacaine. By elevating the upper thoracic spine we could protect against rapid spread of local anaesthetic.

The patient was positioned in the left lateral position with a shoulder wedge to raise the upper thoracic spine. A "through needle" technique was used. At the L3–4 interspace, 2 ml of 0.5% hyperbaric bupivacaine with fentanyl 12.5 μg was injected intrathecally using a 25-gauge pencil point spinal needle. The spinal needle was withdrawn and the epidural catheter was gently inserted. Blood could not be aspirated through the catheter. The patient was then turned to the full right lateral position, again with a shoulder wedge.

After 20 min the block had extended to T9. A test dose of 3 ml of 0.5% bupivacaine was given via the epidural catheter. Five minutes later the block was assessed again and further increments of epidural bupivacaine were administered over 10 min until a total of 8 ml of 0.5% bupivacaine had been given. Forty minutes after the spinal injection, the block had extended to T2 to cold, T3 to pinprick and T5 to light touch. No ephedrine was given and systolic arterial pressure was maintained at 110–140 mm Hg. The efficacy of the block below the level of the lesion was confirmed by loss of ankle clonus and muscle tone in the legs. Interestingly, the patient complained of some dysaesthesia at T12 despite anaesthesia to cutaneous stimulation. Surgery was uneventful and a live female infant was delivered.

After operation the patient was observed closely. As autonomic hyperreflexia could occur in the postoperative period, arterial pressure was assessed regularly and the patient was instructed to report any severe headaches. The regional block receded over a "normal" time course and neurological assessment confirmed that no new deficit had developed. The epidural catheter was left *in situ* in the event that it was required to control a hyperreflexic episode, but was removed after 12 h.

The patient made an uncomplicated recovery from her surgery and was discharged home 5 days later.

Discussion

Neurological deficits in patients with previously unknown and asymptomatic AVM have been reported after epidural[11–13] and spinal[14] anaesthesia in pregnant[13] and non-pregnant patients.[11 12 14] These deficits can be devastating and permanent. However, in each of these reports, cord ischaemia was suspected to have caused the neurological deficit. In our patient, spinal cord haemorrhage had already occurred. Our principal concern was to prevent further neurological damage and we suspected that, although a critical change in spinal cord haemodynamics could result in cord ischaemia, the greater risk was a re-bleed from her spinal cord lesion.

Regional or general anaesthesia could have been used. Both techniques carried potential risks. Regional anaesthesia can be associated with hypotension, especially when the onset of block is rapid. Epidural pressure may also be increased by injection of fluid into the spinal canal. Huselmeyer and White found that injecting 10 ml of 2% lidocaine over 30 s generated a mean increase in epidural pressure of 28.1 cm H_2O and in one patient produced a peak elevation of 73 cm H_2O.[15] The combination of hypotension and increased epidural pressure may cause a critical decrease in perfusion pressure of an already compromised segment of cord, and treating hypotension with vasoconstricting agents could worsen cord ischaemia.

However, with a combined spinal–epidural technique, large volumes of epidural local anaesthetic are not usually required, minimizing any change in epidural pressure. In addition, by using a low dose of intrathecal local anaesthetic and carefully positioning the patient, onset of block could be controlled, minimizing haemodynamic instability. Indeed, during surgery, no vasoactive agents were necessary.

Regional anaesthesia may also cause haemorrhage. As the site of the AVM was known, direct trauma to the lesion itself was unlikely, but trauma to an epidural vein was possible. Extensive AVM generate high flow rates and can enlarge epidural veins along the whole length of the spinal canal.[8] Disruption of an "arterialized" vein could result in a significant epidural haematoma. However, in this instance, the lesion was small and therefore the epidural vessels were unlikely to be enlarged.

Haemorrhage has been reported after diagnostic lumbar puncture. Loss of CSF from the dural sac can change spinal cord anatomy and place AVM under tension. However, with a 25-gauge pencil point needle, the incidence of CSF leak sufficient to cause a postdural puncture headache is approximately 1%,[16] and therefore the risk of producing significant tension on a spinal lesion would probably be much lower than this.

General anaesthesia was the alternative technique. We considered that the risk of further haemorrhage was greater with general anaesthesia because of the potential for hypertension, particularly during induction and intubation. Suppression of the hypertensive response to intubation with high doses of opioids or short-acting antihypertensive agents could have been used, but these techniques might themselves cause problems. A high-dose opioid technique would have compromised the standard rapid sequence induction which would have been modified to avoid using succinylcholine (suxamethonium) because of potential hyperkalaemia. However, in this patient, who was scored as Mallampati grade 1 and was adequately starved, the increased risk of aspiration would have been small. Using antihypertensive agents might have caused a period of rebound hypotension with the associated risk of cord ischaemia, particularly as deep anaesthesia would have been required to suppress autonomic hyperreflexia.

Autonomic hyperreflexia is a condition characterized by a disordered autonomic response to a stimulus below the level of a spinal cord injury. The common features are episodes of severe hypertension with or without reflex bradycardia, headache and occasionally profuse sweating. The higher the level of the spinal injury, the greater the risk of autonomic hyperreflexia. In patients with a T7 lesion there is an 85% incidence of autonomic hyperreflexia.[17] Episodes may start any time from 3 months to 12 yr after the injury has occurred.[18] By the time of surgery, our patient had not had a hyperreflexic episode. However, the lesion had developed recently and surgery would be a potent stimulus. General anaesthesia does not reliably control autonomic hyperreflexia unless deep anaesthesia is used, while regional anaesthesia, particularly spinal anaesthesia, does.[18]

Trying to quantify these relative risks is almost impossible with little literature published. It must be remembered that regional anaesthesia is being performed regularly in patients who have undiagnosed lesions without problems. In this instance we felt that because the AVM was small and had already bled, the risks from general anaesthesia were at least as great as those from regional anaesthesia and therefore after discussion with the patient, we opted for regional anaesthesia.

We remain cautious about using regional anaesthesia in the presence of an AVM, and would always advise careful assessment of the potential benefits. In this particular instance, we have reported the successful management of a primiparous breech delivery by Caesarean section under combined spinal–epidural anaesthesia of a patient who had become paraplegic at 22 weeks' gestation secondary to haemorrhage in the spinal cord.

References

1. Barnes JE, Abbott KH. Cerebral complications incurred during pregnancy and the puerperium. *American Journal of Obstetrics and Gynecology* 1961; **82**: 192–207.
2. Barno A, Freeman DW. Maternal deaths due to spontaneous subarachnoid hemorrhage. *American Journal of Obstetrics and Gynecology* 1976; **125**: 384–392.
3. Miller HJ, Hinckley CM. Berry aneurysms in pregnancy: A ten year report. *Southern Medical Journal* 1970; **63**: 279–285.
4. Berg CJ, Atrash HK, Koonin LM, Tucker M. Pregnancy-related mortality in the United States, 1987–1990. *Obstetrics and Gynecology* 1996; **88**: 161–167.
5. *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1991–1993*. London: HMSO.
6. Krayenbühl H, Yaşargil MG. Die varicosis spinalis und ihre behandlung. *Schweizer Archiv fur Neurologie, Neurochirurgie und Psychiatrie* 1963; **92**: 74–92.
7. Pia HW, Vogelsang H. Diagnose und therapie spinaler angiome. *Deutsch Zeitschrift für Nervenheilkunde* 1965; **187**: 74–96.
8. Symon L, Kuyama H, Kenadall B. Dural arteriovenous malformations of the spine. Clinical features and surgical results in 55 cases. *Journal of Neurosurgery* 1984; **60**: 238–247.
9. Pia HW. Diagnosis and treatment of spinal angiomas. *Acta Neurochirurgica* 1973; **28**: 1–12.
10. Ong BY, Littleford J, Segstro R, Paetkau D, Sutton I. Spinal anaesthesia for caesarean section in a patient with a cervical arteriovenous malformation. *Canadian Journal of Anaesthesia* 1996; **42**: 1052–1058.
11. Gemma M, Bricchi M, Grisoli M, Vinintini S, Pareyson D, Schirlanzoni A. Neurologic symptoms after epidural anaesthesia. Report of three cases. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 742–743.
12. Sghirlanzoni A, Gemma M, Pareyson D, Cimino C, Boiardi A. Spinal arteriovenous fistula. A possible cause or paraparesis after epidural anaesthesia. *Anaesthesia* 1989; **44**: 831–833.
13. Hirsch NP, Child CS, Wijetilleka SA. Paraplegia caused by spinal angioma—possible association with epidural analgesia. *Anesthesia and Analgesia* 1985; **64**: 937–940.
14. Warner DO, Danielson DR, Restall CJ. Temporary paraplegia following spinal anesthesia in a patient with a spinal cord arteriovenous malformation. *Anesthesiology* 1987; **66**: 236–237.
15. Huselmeyer RP, White DC. Lumbar extradural injection pressures in pregnant women. *British Journal of Anaesthesia* 1980; **52**: 55–60.
16. Carson D, Serpell M. Choosing the best needle for diagnostic lumbar puncture. *Neurology* 1996; **47**: 33–37.
17. Colachis SC. Autonomic hyperreflexia with spinal cord injury. *Journal of the American Paraplegia Society* 1992; 15: 171–186.
18. Hambly PR, Martin B. Anaesthesia for chronic spinal cord lesions. *Anaesthesia* 1998; **53**. 273–289.

British Journal of Anaesthesia 1998; **81**: 979–981

Large goitre causing difficult intubation and failure to intubate using the intubating laryngeal mask airway: lessons for next time

H. G. WAKELING, A. ODY AND A. BALL

Summary

A 63-yr-old woman was anaesthetized for sub-total thyroidectomy. The thyroid gland was large, deviating the trachea to the right and causing 30% tracheal narrowing at the level of the suprasternal notch. Mask ventilation was easy but laryngoscopy was Cormack and Lehane grade 3. Despite being able to see the tip of the epiglottis, tracheal intubation was impossible. An intubating laryngeal mask was inserted and although the airway was clear and ventilation easy, it was not possible to intubate the trachea either blindly or with the fibreoptic bronchoscope. Tracheal intubation was eventually achieved using a 6.5-mm cuffed oral tracheal tube via a size 4 laryngeal mask under fibreoptic control. We describe the case in detail and discuss the use of the intubating laryngeal mask, its potential limitations and how to optimize its use in similar circumstances. (*Br. J. Anaesth.* 1998; **81**: 979–981).

Keywords: intubation tracheal; intubation tracheal, complications; equipment, masks anaesthesia

Difficulty with intubation may be caused by an enlarged thyroid gland producing tracheal deviation or compression, or both. The laryngeal mask airway has been recognized as a useful adjunct during difficult intubation. It appears in the American Society of Anesthesiologists' difficult airway algorithm, both as an emergency airway and the conduit of choice for the fibreoptic bronchoscope.[1] The intubating laryngeal mask airway (ILMA, Fastrach, Intavent, UK) recently became available. It is a laryngeal mask airway which has been adapted extensively to enable blind intubation of the trachea using an especially modified tracheal tube.[2] Brian and colleagues found this device to be useful for difficult intubation; easy ILMA ventilation and reliable tracheal intubation were achieved in a group of patients with known or predicted difficult intubation.[3]

We describe the airway management of a patient with a large goitre with particular emphasis on the use and potential limitations of the ILMA, with suggestions for optimizing ILMA technique.

Case report

A 63-yr-old retired nurse presented for thyroidectomy with a thyroid goitre of approximately 30 yr. She was euthyroid after treatment with propylthiouracil. Past medical history included hypertension and palpitations when she was hyperthyroid. Medication included propranolol LA 160 mg daily and propylthiouracil 150 mg bid. She was allergic to tetracycline. She had undergone general anaesthesia uneventfully on three previous occasions. She had no stridor, hoarseness or difficulty breathing and was not a smoker. There was no history of gastro-oesophageal reflux.

Airway assessment revealed prominent incisor teeth and some crowned molars. Her mouth opened well and she had a Mallampati grade I upper airway. She had somewhat restricted neck extension but the trachea did not appear to be clinically deviated. A thoracic inlet x-ray showed tracheal deviation to the right, maximal just above the suprasternal notch, with approximately 30% narrowing of the trachea in its anterioposterior and transverse diameters at this point (fig. 1).

Cardiorespiratory assessment was normal with a slow regular heart rate of 56 beat min^{-1} and arterial pressure of 170/80 mm Hg. Heart sounds were normal. There was no stridor. Chest expansion and breath sounds were normal. Full blood count, urea and electrolyte concentrations, and thyroid function tests were normal. She was premedicated with temazepam 20 mg and metoclopramide 10 mg orally.

A 16-gauge i.v. cannula was inserted into the left forearm and an infusion of Hartmann's solution commenced. Full non-invasive monitoring was used, including ECG, arterial pressure, oxygen saturation, inspired oxygen and end-tidal carbon dioxide before induction of anaesthesia. Previous discussion with the surgeon had excluded the need to stimulate the recurrent laryngeal nerve. Anaesthesia was induced with fentanyl 200 μg and thiopental (thiopentone) 400 mg. Mask ventilation was easy and vecuronium 8 mg was given to facilitate intubation. Anaesthesia was maintained with 1% isoflurane and 50% nitrous oxide in oxygen. The patient's head was placed on two pillows and the neck extended as far as the restriction allowed. Direct laryngoscopy using a size 3 MacIntosh blade revealed only the tip of the epiglottis. It was not possible to pass a gum-elastic bougie into the trachea. A size 4 McCoy laryngoscope was used but this did not improve the view. Between intubation attempts, the patient's lungs

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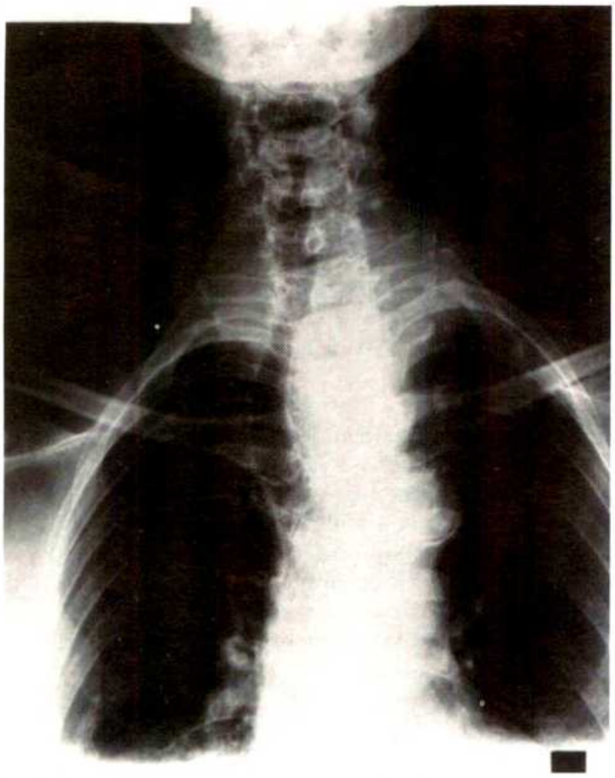

Figure 1 Thoracic inlet x-ray showing tracheal deviation caused by the large thyroid goitre.

were ventilated uneventfully using a face mask and adequate anaesthetic depth was maintained.

An ILMA size 4 was inserted easily into the hypopharynx and 30 ml of air were placed in the cuff. The breathing system was connected to the ILMA and easy, unobstructed manual ventilation established. The position of the ILMA was adjusted until an optimal seal was established. An 8-mm id ILMA tracheal tube was advanced down the ILMA in the position of optimal seal. The tracheal tube passed into the oesophagus on this and all other occasions without resistance. The position of the ILMA was adjusted several times. First, the mask was inserted further so that the first black line was at the level of the teeth. Second, the ILMA was withdrawn so that the fourth and then sixth lines were level with the teeth. Third, the ILMA was rotated gently to the right to compensate for the deviation of the trachea, and finally size 3 and then size 5 ILMA were tried, all without success. A fibreoptic bronchoscope loaded with a tracheal tube was then inserted via the ILMA. Passage of the fibrescope was extremely difficult and we were unable to see the larynx. This was partly because the epiglottic elevating bar (EEB) obscured the view and prevented the bronchoscope tip from passing sufficiently anterior. Despite trying to alter the position of the ILMA, it was impossible to see the laryngeal inlet.

A standard size 4 laryngeal mask was then inserted and ventilation established. It was eventually possible to see a swollen laryngeal opening using the fibreoptic bronchoscope via the LMA. The bronchoscope was inserted to reveal the tracheal bifurcation and a 6.5-mm id tracheal tube, already mounted, was railroaded over the scope. Tracheal intubation was confirmed by end-tidal carbon dioxide measurement and auscultation. The tracheal tube and LMA were replaced with an 8-mm id tracheal tube over a gum-elastic bougie. Throughout this period, the patient remained stable with heart rate 60–70 beat min^{-1} and systolic arterial pressure 110–150 mm Hg. Oxygen saturation remained at 97–99% throughout.

Thyroidectomy was performed without complication. I.v. dexamethasone 10 mg was given to reduce glottic swelling. The patient was sedated and ventilated overnight in the intensive care unit. The following day, sedation and ventilation were weaned off. On deflating the tracheal tube cuff, an audible leak was heard and the tube was removed uneventfully. I.v. dexamethasone was continued for 24 h but there were no further airway difficulties.

Discussion

Patients with large goitres are considered to be more likely to present difficulty at intubation, particularly if the goitre has produced tracheal deviation or has retrosternal extension.[4] In this case, there was radiological evidence of tracheal deviation which was asymptomatic. The patient had prominent incisor teeth and restricted neck extension. She was Mallampati grade I. Once the degree of intubation difficulty was established, several options were considered. Postponing the procedure and reducing the gland with radio-iodine was a possibility, but this can cause acute swelling and airway compromise. A laryngeal mask airway (LMA) was considered but there was a risk that tracheal intubation could be required urgently, as has been reported previously.[5]

Fibreoptic placement of the tracheal tube via a standard LMA was difficult because the larynx was deviated to the right and the laryngeal inlet had tipped forwards. To enter the laryngeal inlet, the bronchoscope had to be angled steeply anteriorly and to the right on emerging from the LMA, and then caudally when the posterior aspect of the laryngeal inlet had been passed.

The ILMA is a recently available device for blindly intubating the trachea.[2 3 6] It consists of a modified LMA attached to a curved stainless steel tube. The curvature of the tube was developed using a series of sagittal magnetic resonance images (MRI) of the head and neck. The consequent tube curvature represents the best fit from the MRI series. The aperture bars have been replaced by the EEB which lifts the epiglottis up out of the way during tracheal tube placement. In addition, a 20° tracheal tube guiding ramp has been incorporated immediately behind the EEB to guide the tube more anteriorly.[2]

Interestingly, although tracheal intubation with the ILMA was not achieved in this case, ventilation via the ILMA was easy with all three sizes. In two recent ILMA studies, ventilation was easy in all 250 patients via the ILMA.[3 6] This is important as we have not seen any reports of inability to ventilate in either our own series or in the literature. One of the preliminary studies clearly demonstrated a learning curve in gaining expertise with the use of the ILMA.[6] This case report arose from our seventh use of the device. It represents one of only two failures in 56 uses to date.

There have been no reports of ILMA use in patients with distorted laryngeal anatomy. Although difficult intubation conditions have been described in two large preliminary studies[3 6] and in a recent triple case report,[7] none has described an altered laryngeal position. The ILMA may have limited use in cases such as this where the laryngeal position has been altered significantly by disease.

However, there are some lessons that we have learnt from this case, subsequent cases and discussion with the inventor. First, the ILMA is for use with the head in the neutral position. We kept the head in the "sniffing" position throughout. This would have decreased the anterior angle of projection of the tracheal tube from the ILMA and directed it more towards the oesophagus. Second, with further experience we have found that lifting the ILMA handle such that the rim of the proximal end of the ILMA tube lies in the horizontal plane improves intubation success. This presumably increases the anterior projection angle, reducing the likelihood of oesophageal intubation.

We were unable to see the larynx using the fibreoptic bronchoscope via the ILMA. It was not possible to direct the bronchoscope anteriorly enough to reach the laryngeal inlet because of the EEB. The inventor suggested that this problem may be avoided by inserting the tracheal tube to the horizontal line (indicating that the tube tip lies at the EEB) and advancing it 1.5 cm to lift the EEB before inserting the bronchoscope. It may have been possible to locate the larynx fibreoptically with this approach as this was achieved through a standard LMA.

The inventor also suggested holding a second ILMA of the same size externally, exactly parallel to the inserted device. This permits estimation of the position of the EEB. The EEB should be cephalad to (i.e. above) but within 2 cm of the thyroid prominence, which approximates to the laryngeal inlet. By holding the second ILMA alongside, the inserted device can be manoeuvred to achieve the alignment described.

In summary, this case of difficult intubation arose from deviation of the laryngeal inlet anteriorly and laterally because of a large thyroid goitre. The ILMA provided a means of easy, unobstructed ventilation of the patient's lungs whichever size was used and despite the airway abnormalities. But failure to intubate with the device blind or with a fibreoptic bronchoscope occurred; inexperience may have contributed to this failure. However, this is the first case report of attempted ILMA use in the presence of abnormal laryngeal position. Further experience with the device in such cases is needed to determine if abnormal lower airway position represents a significant limitation to the usefulness of this device for tracheal intubation.

References

1. Benumof JL. Laryngeal mask airway and the ASA difficult airway algorithm. *Anesthesiology* 1996; **84**: 686–699.
2. Brain AIJ, Verghese C, Addy EV, Kapila A The intubating laryngeal mask. I: development of a new device for intubation of the trachea. *British Journal of Anaesthesia* 1997; **79**: 699–703.
3. Brain AIJ, Verghese C, Addy EV, Kapila A, Brimacombe J The intubating laryngeal mask. II· a preliminary clinical report of a new means of intubating the trachea. *British Journal of Anaesthesia* 1997; **79**: 704–709.
4. Sebel PS. Anaesthesia for thyroid and parathyroid disease. In Nimmo WS, Rowbotham DJ, Smith G, eds. *Anaesthesia* Oxford: Blackwell Scientific Publications, 1994.
5. Hobbiger HE, Allen JG, Greatorex RG, Denny NM. The laryngeal mask for thyroid and parathyroid surgery. *Anaesthesia* 1996; **51**: 972–974.
6. Kapila A, Addy EV, Verghese C, Brain AIJ. The intubating laryngeal mask airway: an initial assessment of performance *British Journal of Anaesthesia* 1997; **79**· 710–713
7. Parr MJA, Gregory M, Baskett PJF. The intubating laryngeal mask. Use in failed and difficult intubation. *Anaesthesia* 1998, **53**: 343–348.

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CITATION CLASSIC

Commentary

Spence AA, Smith G. Postoperative analgesia and lung function: a comparison of morphine with extradural block. *British Journal of Anaesthesia* 1971; **43**: 144–148.

This study compares the effect of two postoperative pain control methods, i.m. morphine and intermittent epidural bupivacaine, on respiratory function in a group of 21 patients after upper abdominal surgery. The epidural method was found to have a significant beneficial effect, producing better arterial oxygenation, lower ventilatory frequencies, a larger tidal volume and a lower incidence of postoperative pneumonia. The extent of impairment of respiratory function seen over the first 5 days after operation is significant. Vital capacity was reduced to one-third of the preoperative value on the first day after operation and was only 60% of the preoperative value by day 5.

It would not be surprising to find a study comparing the postoperative effects of epidural bupivacaine and i.m. morphine on respiratory function in an anaesthetic journal in the 1990s. However, Spence and Smith's study describes their use in the early 1970s. It is important when reviewing such a study to put it in the context of the clinical practice at that time before analysing its historical significance. The range of drugs and techniques available for postoperative analgesia was limited essentially to i.m. opioids (morphine, pethidine and diamorphine). Bupivacaine had been introduced into clinical practice in 1968 and merited only brief mention in two standard UK textbooks published in 1970. The use of epidural analgesia was essentially limited to a relatively small number of centres providing an obstetric service. It is interesting also to note that the surgical procedures have changed over the same time period. The introduction of H_2 antagonists means that vagotomy and pyloroplasty is an operation performed only rarely, but in the 1960s and 70s it was the "bread and butter" of general surgical lists.

The respiratory changes described in this article had been noted previously and have become established subsequently in anaesthetic practice. However, their significance is not always remembered in postoperative care after major abdominal surgery. Indeed, in 1992, Reeder and colleagues[1] demonstrated that in a group of patients who had undergone abdominal aortic surgery, there was significant impairment of oxygenation, as measured by continuous pulse oximetry, during the first 5 nights after operation. Median time spent with Sp_{O_2} <90% for all patients studied on the third night after operation was almost 50%.

Investigation of pulmonary function in this study was thorough, and included chest x-ray, arterial and expired gas analysis and spirometry. The incidence of postoperative pneumonia was high (70% in the morphine group) but perhaps not surprising in a group of patients most of whom (19 of 21) were smokers and hypoventilating. The criteria used to define pneumonia in this study are still generally applicable and it is notable that all patients with pneumonia fulfilled two or more of the criteria. In comparison, a recent study[2] of 200 morbidly obese patients undergoing gastric surgery found an incidence of respiratory complications after operation of approximately 6%. This occurred in a population that would be expected to be at high risk of such complications.

What has changed in the postoperative management of patients undergoing major abdominal surgery since this article was published that may have resulted in such improvements? There have been several areas which may have contributed to this, including the wider use of postoperative oxygen therapy, monitoring (particularly pulse oximetry[3]) and methods of drug delivery. In the case of methods of delivery, patient-controlled analgesia (PCA) systems or continuous thoracic epidural infusion have become the standard choice after upper abdominal surgery.[4] Morphine is still the most widely used drug for PCA. It is interesting to note that in the original article, the authors consider they were using a relatively high dose of morphine in the first 24 h; 20 mg in the perioperative period and a mean of 26 mg after operation. This would be considered a very modest dose in most PCA studies after upper abdominal surgery. For example, the study of George and colleagues[5] used fentanyl 2 μg kg^{-1} in the peroperative period and a mean of 92 mg of morphine in the first 24 h.

There has been a change in drug use epidurally with the move initially to lower concentrations of bupivacaine and subsequently to the addition of opioids, now most commonly fentanyl. George and colleagues compared the effects of epidural fentanyl 10 μg ml^{-1}–0.2% bupivacaine mixture with PCA morphine i.v. on respiratory function during the first 24 h after upper abdominal surgery. Both techniques demonstrated a decrease in FVC, FEV_1 and PEFR and increased Pa_{CO_2}, but the effects were greater with PCA.

Another element of this type of study that has changed since this original publication is assessment of patient pain. The widespread introduction of acute pain services in the 1990s has led to the shift in emphasis from "PRN morphine i.m." towards titration of postoperative analgesia to individual requirements. This has been achieved by regular assessment of patient pain using visual analogue scores and has helped to minimize the risk of getting into the cycle of: severe pain with hypoventilation, treated with a large dose of morphine i.m., leading subsequently to over sedation and a period of respiratory depression. This cycle of events is likely to have been involved in the high incidence of respiratory complications in Spence and Smith's study.

The conclusion from this study, that the choice of postoperative analgesic regimen has a major influence on the incidence and pattern of postoperative respiratory complications, is still relevant to current practice. Championing of epidural analgesia as a method likely to reduce the incidence of respiratory complications has been borne out by subsequent research.

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References

1. Reeder MK, Goldman MD, Loh L, Muir AD, Foex P, Casey KR, McKenzie PJ. Postoperative hypoxaemia after major abdominal vascular surgery. *British Journal of Anaesthesia* 1992; **68**: 23–26.
2. Goulding ST, Hovell BC. Anaesthetic experience of vertical banded gastroplasty. *British Journal of Anaesthesia* 1995; **75**: 301–306.
3. Wheatley RG, Somerville ID, Sapsford DJ, Jones JG Postoperative hypoxaemia: comparison of extradural, i m. and patient-controlled opioid analgesia. *British Journal of Anaesthesia* 1990; **64**: 267–277.
4. Peacock JE, Dale S. Patient controlled analgesia. *Current Opinion in Anesthesiology* 1996, **9**: 313–317.
5. George KA, Wright PMC, Chisakuta AM, Rao NVS. Thoracic epidural analgesia compared with patient controlled intravenous morphine after upper abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1994, **38**. 808–812.

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Brit. J. Anaesth. (1971), **43**, 144

POSTOPERATIVE ANALGESIA AND LUNG FUNCTION: A COMPARISON OF MORPHINE WITH EXTRADURAL BLOCK

BY

A. A. SPENCE AND G. SMITH

SUMMARY

Twenty-one patients for vagotomy with gastroenterostomy or pyloroplasty were allocated randomly to postoperative analgesia with either morphine by injection or continuous extradural nerve block. In terms of clinical assessment and A–a P_{O_2} difference measured before and after operation, extradural nerve block was found to reduce the degree of postoperative lung dysfunction. It is concluded that the conventional use of narcotics for postoperative analgesia increases the risk of lung morbidity.

Postoperative hypoxaemia in the absence of hypoventilation has been observed by many investigators and is most marked following upper abdominal and thoracic surgery (Diament and Palmer, 1966). In the first few hours after operation, hypoxaemia is thought to be due chiefly to regional misalignment of ventilation and perfusion (Nunn and Payne, 1962; Conway and Payne, 1963). Diament and Palmer (1967) have shown that, by the end of 24 hours, frank shunting of blood past collapsed alveoli is the dominant factor, although a ventilation/perfusion component may be demonstrated (Georg, Hornum and Mellemgaard, 1967). It is known that these derangements need not be accompanied by radiological changes in the lung (Bendixen, Hedley-Whyte and Laver, 1963; Hamilton et al., 1964).

Although the factors which produce postoperative alveolar collapse are not fully evaluated, it is widely assumed that pain plays an important role by impairing coughing, limiting lung expansion (Beecher, 1933; Schwartz, Dale and Rahn, 1957; Mead and Collier, 1959) and reducing functional residual capacity (Anscombe, 1957). It is a matter of everyday observation that opiate analgesia, although administratively simple and therefore commonly used, may not produce complete pain relief. Continuous extradural nerve block has been shown to produce complete analgesia (Simpson et al., 1961) and to facilitate better lung expansion (Bromage, 1955), but is time-consuming and demands special skill. This study was designed to compare the effect of these two approaches to postoperative pain relief on lung function with special reference to arterial oxygenation.

PATIENTS AND METHODS

Investigations were made on 21 male patients in the age range 21–50 years, scheduled for vagotomy with gastroenterostomy or pyloroplasty, but otherwise in good health and within ± 10 per cent of the expected body weight.

The patients were given morphine 10 mg, atropine 0.6 mg and droperidol 5 mg, 1 hour before operation. Anaesthesia was induced with thiopentone followed by suxamethonium and, after orotracheal intubation, maintained with nitrous oxide, supplemented by morphine 10 mg and tubocurarine. At the end of anaesthesia, the tubocurarine was reversed with neostigmine combined with atropine. Extubation was preceded by bronchial and pharyngeal suction using a Pinkerton catheter.

The operation was performed through a standard right paramedian incision. All patients came from the same surgical unit and were nursed in the same ward. At the end of each operation, the patient was allocated randomly to one of two postoperative analgesic regimes:

(1) Morphine 10 mg by intramuscular injection given on demand by the Sister or Senior Ward Staff Nurse. [The mean dose of morphine was 26 mg (range 20–30 mg) on day 1 and 18 mg (range 10–20 mg) on day 2.]

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(2) Continuous extradural spinal nerve block administered by investigators.

At the completion of the operation, but before the end of anaesthesia, a catheter was inserted in the thoracic extradural space through the T7–8 interspace. For 48 hours after operation, bupivacaine 0.5 per cent (with adrenaline 1:300,000) was injected intermittently to achieve a block of the wound segments. In practice, the blocks achieved loss of pinprick sensation from segments T4 to T12. The volume of each injection was usually in the range 5–7 ml and repeat injections were made every 2 hours approximately. Criteria for repeat injections were subjective discomfort or the return of pinprick sensation.

All patients had routine chest physiotherapy once per day after operation. This consisted of diaphragmatic breathing, lower costal breathing, percussion-assisted drainage and assisted coughing. The whole procedure lasted for about 20 minutes. If on clinical grounds those in charge of the patient considered that postoperative pneumonia had occurred, physiotherapy was increased in frequency and antibiotics were administered. In this context, chest infection was defined as:

(a) pyrexia of more than 5 hours duration accompanied by progressive auscultatory changes, or
(b) radiological changes, or
(c) purulent sputum plus pyrexia.

In fact, where such a decision was reached, more than one of the prearranged criteria were present.

INVESTIGATIONS OF PULMONARY FUNCTION

Pre-operatively and on days 1, 2 and 5 after operation, the following were carried out:

(1) Chest X-ray.
(2) Arterial blood analysis: Pa_{O_2}, Pa_{CO_2} and pH.
(3) Expired gas analysis; volume ($\dot{V}_E$), respiratory frequency (f), fractional concentration of oxygen and carbon dioxide.
(4) Spirometry: vital capacity and timed forced vital capacity.

Blood sampling and gas collection were performed simultaneously. All patients breathed room air at all times. Alveolar-arterial P_{O_2} difference [A–a D_{O_2} (mm Hg)] was calculated as follows:

$$\text{A–a } D_{O_2} = P_{A_{O_2}} - Pa_{O_2}$$

$$\text{where } P_{A_{O_2}} = P_{I_{O_2}} - Pa_{CO_2}\left[\frac{F_{I_{O_2}} - F_{E_{O_2}}}{F_{E_{CO_2}}}\right]$$

(Filley, MacIntosh and Wright, 1954)

Physiological deadspace (V_D) was calculated using the Bohr equation and was expressed as a fraction of tidal volume (V_T). All blood-gas values were corrected, where necessary, for temperature using the nomograms of Kelman and Nunn (1966). Pulmonary function tests were performed in an identical order and manner for all patients studied. All tests were made by the investigators. During tests, the patients were in the sitting position.

RESULTS

Table I presents details of the patients studied. At 48 hours after operation, 7 of the 10 patients in the morphine group and 2 of 11 in the extradural group had a postoperative pneumonia.

Table II shows the results of the blood gas measurements together with calculated values for A-a D_{O_2}, oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_{CO_2}$). In terms of A–a D_{O_2}, there is a significant difference between the two groups on day 1 ($P<0.02$), day 2 ($P<0.01$) and day 5 ($P=0.01$) after operation. By day 5, the mean value of the extradural group had returned to the pre-operative level, whereas the morphine group still showed evidence of hypoxaemia (mean A–a $D_{O_2}=25$ mm Hg). Parallel changes occurred in arterial P_{O_2} measurements. There was no important difference between the groups in arterial P_{CO_2} measurements in the first two postoperative days, although the mean values after operation were lower than before operation. On day 5, the mean value for the extradural group was significantly higher than the mean value for the morphine group ($P<0.05$).

An apparent fall in mean $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in the extradural group on postoperative days 1 and 2 (i.e. during the period of the block) was not statistically significant when compared with the pre-operative mean for that group or the corresponding values for the morphine group.

Table III lists the results of spirometry together with calculated V_D/V_T ratios and FEV_1/FVC per cent. The first two postoperative days were characterized by a fall in tidal volume with an

TABLE I

Mean age, height and weight, smoking habits and incidence of postoperative pneumonia for the two patient groups studied. Standard errors of the mean are given where appropriate.

Treatment group	Number	Age (yr)	Height (cm)	Weight (kg)	Ratio smokers : non-smokers	Postoperative pneumonia
Morphine	10	37 ±3.4	175 ±1.1	62 ±3.5	9 : 1	7
Extradural	11	42 ±3.7	176 ±1.4	66 ±2.3	10 : 1	2

TABLE II

Arterial P_{O_2} and P_{CO_2}, alveolar-arterial P_{O_2} difference, oxygen consumption and carbon dioxide output. Mean values and standard errors of the mean for morphine (M) and extradural (E) patient groups.

Time of measurement	Pa_{O_2} (mm Hg)		Pa_{CO_2} (mm Hg)		A-a D_{O_2} (mm Hg)		$\dot{V}_{O_2}$ (ml STPD/min)		$\dot{V}_{CO_2}$ (ml STPD/min)	
	M	E	M	E	M	E	M	E	M	E
Before operation	93.0 ±3.0	94.8 ±4.0	37.1 ±1.0	38.3 ±0.5	7.8 ±2.9	6.6 ±2.6	300 ±14	325 ±26	234 ±13	262 ±20
Postop. day 1	69.3 ±4.4	82.8 ±2.3	35.2 ±0.9	34.1 ±0.9	33.3 ±4.9	19.4 ±4.2	325 ±25	299 ±17	246 ±12	224 ±14
Postop. day 2	68.0 ±3.2	81.6 ±3.4	35.1 ±0.9	33.7 ±0.9	35.7 ±3.3	22.2 ±4.0	328 ±21	279 ±18	258 ±15	228 ±14
Postop. day 5	83.5 ±5.4	92.3 ±3.3	33.1 ±1.2	36.3 ±0.3	25.3 ±6.6	6.9 ±3.2	313 ±15	309 ±12	263 ±14	234 ±16

increase in minute volume and respiratory frequency which were similar in magnitude for both groups. The mean frequency of 20.7 in the morphine group on day 2 was significantly higher than the corresponding mean of 16.5 in the extradural group ($0.05 > P > 0.025$). There was no significant change in V_D/V_T throughout the study.

Both groups had a marked reduction in vital capacity following operation which, although improving, had not returned to the pre-operative values by day 5. There was no significant difference between the groups for any vital capacity measurement. The mean values for FEV_1/FVC per cent decreased following operation in the morphine group but increased slightly in the extradural group. The difference between the groups was significantly different on day 2 ($P < 0.01$).

X-ray appearances of the lungs did not relate to the degree of hypoxaemia, although evidence of consolidation was found in some of the patients with clinical evidence of pneumonia. After operation, all patients showed radiological evidence of gas under the diaphragm which was absorbed slowly, although still detectable on X-ray at day 5.

DISCUSSION

In this study, we have compared a conventional method of therapy for postoperative pain (morphine 10 mg by injection) with extradural block—a method known to abolish pain. We chose patients having upper abdominal incisions because earlier unpublished observations by one of us (A.A.S.) had established that this group had the highest incidence of postoperative pain and that pain was more or less continuous throughout 48 hours following operation. We attempted to standardize as far as possible all other factors which might influence postoperative lung morbidity: weight, age, medical history, smoking habits and abdominal incision.

The patients who had extradural analgesia were significantly better in terms of clinical assessment and arterial oxygenation than those who had morphine. In 1968 Muneyuki and his colleagues also

TABLE III

Tidal and minute volumes, respiratory frequency, deadspace/tidal volume ratio, vital capacity and FEV_1/FVC per cent. Mean values and standard errors of the mean for morphine (M) and extradural (E) patient groups. All gas volumes at BTPS.

Time of measurement	V_T (ml)		V_E (ml)		Frequency (b.p.m.)		V_D/V_T		Vital capacity (ml)		FEV_1/FVC per cent	
	M	E	M	E	M	E	M	E	M	E	M	E
Before operation	630 ±56	667 ±125	8221 ±561	7140 ±799	13.5 ±0.9	14.0 ±1.2	0.298 ±0.030	0.244 ±0.022	3859 ±209	3924 ±199	80 ±2.3	76 ±3.0
Postop day 1	478 ±32	559 ±75	9976 ±972	8423 ±600	21.1 ±1.9	16.9 ±1.6	0.293 ±0.031	0.252 ±0.020	1232 ±98	1065 ±198	77 ±3.9	83 ±2.5
Postop. day 2	519 ±40	542 ±64	10345 ±803	8146 ±546	20.7 ±1.6	16.5 ±1.6	0.334 ±0.035	0.263 ±0.013	1613 ±112	2035 ±226	70 ±3.2	81 ±2.6
Postop. day 5	659 ±81	642 ±102	9165 ±704	7598 ±360	15.2 ±1.5	13.6 ±1.3	0.235 ±0.018	0.241 ±0.022	2449 ±297	2450 ±492	72 ±2.2	74 ±2.7

studying patients for upper abdominal surgery, compared the effect of extradural nerve block with intravenous pethidine carefully "titrated" against the patients' pain state. Although their study ended at 15 hours after operation, their results may be compared with our findings on day 1. They found no significant difference between extradural block and pethidine in terms of Pa_{O_2} and A–a D_{O_2}. The mean values for Pa_{O_2} (86.6 mm Hg) and A–a D_{O_2} (17.9 mm Hg) in their extradural group are very close to the findings which we report (table II). On an equipotent basis, the dose of narcotic employed by us was approximately nine times that of Muneyuki and his colleagues. Therefore, we conclude that our study highlights the unsatisfactory consequences of the conventional large doses of narcotics in the postoperative period.

By the use of intravenous isotonic solutions, we were able to ensure that the extradural patients did not become hypotensive as a consequence of the technique. There exists the possibility that disturbance of the ventilation perfusion relationship in the lung may be aggravated in patients who have a partial sympathetic block. Although there is no evidence that this is an important factor in the supine patient (de Jong, 1965), it should be pointed out that our patients were sitting up after operation. The absence of a significant change in V_D/V_T during the period of the block is not in keeping with this hypothesis.

We were surprised to find that the postoperative changes in vital capacity were similar in both groups. The order of the changes which we found in the morphine group have been reported previously (Anscombe, 1957). Other workers have described a sparing effect of extradural analgesia on the vital capacity (Bromage, 1955; Simpson et al., 1961), although in both of these studies the selection of patients was less rigorous than in the present study. A possible explanation of our findings is that extradural block may produce considerable, if not complete, motor function loss in the affected segments. Since the lower intercostal and upper abdominal muscles are expiratory in function, there must have been a considerable reduction in expiratory reserve volume. Unfortunately, this was not measured.

Our investigations ended on the 5th postoperative day, by which time most of the patients were regarded as being sufficiently recovered for transfer to convalescence. It is disturbing that the morphine group, at this stage, still exhibited hypoxaemia sufficient to suggest an approximate 10 per cent increase in intrapulmonary shunting. We consider that this prolonged hypoxaemia and the possibility of long-term morbidity arising from such postoperative lung changes merit further attention.

Our radiological studies have confirmed the findings of previous workers that considerable hypoxaemia may exist without detectable X-ray changes. The presence of gas under the diaphragm was an incidental finding and was so consistent that we cannot at present assess its effect. Bevan

(1961) concluded that pneumoperitoneum may be a cause of postoperative pneumonia.

In conclusion, we have shown that the analgesic regime may influence the pattern of postoperative hypoxaemia. Although we accept that the widespread use of continuous extradural nerve block in routine practice is not always feasible, we would advocate that analgesic techniques should be assessed not only in terms of the subjective relief which the patient experiences but also their effect in reducing lung morbidity.

REFERENCES

Anscombe, A. R. (1957). *Pulmonary Complications of Abdominal Surgery.* London: Lloyd-Luke.

Beecher, H. K. (1933). Effect of laparotomy on lung volume: demonstration of a new type of pulmonary collapse. *J. clin. Invest.*, **12**, 651.

Bendixen, H. H., Hedley-Whyte, J., and Laver, M. B. (1963). Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. *New Engl. J. Med.*, **269**, 991.

Bevan, P. G. (1961). Postoperative pneumoperitoneum and pulmonary collapse. *Brit. med. J.*, **2**, 609.

Bromage, P. R. (1955). Spirometry in assessment of analgesia after abdominal surgery: a method of comparing analgesic drugs. *Brit. med. J.*, **2**, 589.

Conway, C. M., and Payne, J. P. (1963). Postoperative hypoxaemia and oxygen therapy. *Brit. med. J.*, **1**, 844.

Diament, M. L., and Palmer, K. N. V. (1966). Postoperative changes in gas tensions of arterial blood and in ventilatory function. *Lancet*, **2**, 180.

—— —— (1967). Venous/arterial pulmonary shunting as the principal cause of postoperative hypoxaemia. *Lancet*, **1**, 15.

de Jong, R. H. (1965). Arterial carbon dioxide and oxygen tensions during spinal block. *J. Amer. med. Ass.*, **191**, 698.

Filley, G. F., MacIntosh, D. J., and Wright, G. W. (1954). Carbon monoxide uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. *J. clin. Invest.*, **33**, 530.

Georg, J., Hornum, I., and Mellemgaard, K. (1967). The mechanism of hypoxaemia after laparotomy. *Thorax*, **22**, 382.

Hamilton, W. K., McDonald, J. S., Fischer, H. W., and Bethards, R. (1964). Postoperative respiratory complications: comparison of arterial gas tensions, radiographs and physical examination. *Anesthesiology,*, **25**, 607.

Kelman, G. R., and Nunn, J. F. (1966). Nomograms for correlation of blood Po_2, Pco_2, pH and base excess for time and temperature. *J. appl. Physiol.*, **21**, 1484.

Mead, J., and Collier, C. (1959). Relation of volume history of lungs to respiratory mechanics in anesthetised dogs. *J. appl. Physiol.*, **14**, 69.

Muneyuki, M., Ueda,, Y., Urabe, N., Takeshita H., and Inamoto A. (1968). Postoperative pain relief and respiratory function in man: comparison between intermittent intravenous injections of meperidine and continuous lumbar epidural analgesia. *Anesthesiology*, **29**, 304.

Nunn, J. F., and Payne, J. P. (1962). Hypoxaemia after general anaesthesia. *Lancet*, **2**, 631.

Schwartz, S. I., Dale, W. A., and Rahn, H. (1957). Deadspace rebreathing tube for prevention of atelectasis. *J. Amer. med. Ass.*, **166**, 1248.

Simpson, B. R., Parkhouse, J., Marshall, R., and Lambrechts, W. (1961). Extradural analgesia and the prevention of postoperative respiratory complications. *Brit. J. Anaesth.*, **33**, 628.

British Journal of Anaesthesia 1998; **81**: 989–996

CORRESPONDENCE

Not all crystalloid solutions are equal

Editors,—I read with interest the article by Ruttmann, James and Aronson[1] concerning haemodilution with hydroxethyl starch and normal saline. However, I disagree with their conclusion that they have shown that haemodilution *per se* exerted a procoagulant effect in both groups. Instead, I propose that their conclusion should be that they demonstrated that haemodilution *with normal saline* resulted in these changes. They did not state that the hydroxyethyl starch was dissolved in 0.9% sodium chloride, although that is the usual formulation. If this were the case, one would expect the changes that were found in the normal saline group to be present also in the hydroxyethyl starch group, just as they described.

Normal saline has a pH of 6.1, osmolality of 308 mosmol kg^{-1}, sodium ion concentration of 154 mEq $litre^{-1}$ and chloride ion concentration of 154 mEq $litre^{-1}$. As would be expected, post-infusion serum values reflected those of i.v. fluids, especially when the latter were administered rapidly.[2] Therefore, after normal saline has been infused, there is an increase in serum sodium, chloride and osmolality, and a decrease in serum pH. Administration of another crystalloid, such as Hartmann's solution, results in different serum values[3] because Hartmann's solution has a higher pH (6.5), lower osmolality (273 mosmol kg^{-1} calculated and 254 mosmol kg^{-1} measured), and different electrolyte concentrations compared with normal saline.

The procoagulant changes reported in their article could have been caused by the changes in serum electrolyte concentration, osmolality or pH associated with infusion of normal saline, rather than by haemodilution. It would be interesting to know if the changes in coagulation reported in this article could have been avoided by the use of a different crystalloid such as Hartmann's solution.

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1. Ruttman TG, James MFM, Aronson I. *In vivo* investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation. *British Journal of Anaesthesia* 1998; **80**: 612–616.
2. Veech RL. The toxic impact of parenteral solutions on the metabolism of cells: a hypothesis for physiological parenteral therapy. *American Journal of Clinical Nutrition* 1986; **44**: 519–551.
3. Coran AG, Ballantine TV, Horwitz DL, Herman CM. The effect of crystalloid resuscitation in hemorrhagic shock on acid–base balance: a comparison between normal saline and Ringer's lactate solutions. *Surgery* 1971; **69**: 874–880.

Editor,—We thank Dr Williams for her interest in our article on haemodilution and are grateful for the opportunity to reply. First, we confirm the comment that the hydroxyethyl starch is dissolved in 0.9% sodium chloride. Second, we ourselves considered the possibility that the haemodilution effect may have been a result of the nature of the crystalloid solution used, particularly the pH variability and perhaps the temperature. The original work on haemodilution published by Tocantins, Carroll and Holburn[1] suggested that the nature of the diluent solution was unimportant. They investigated the effect on coagulation of buffered beef fibrinogen, 5% glucose, acacia, buffered 0.85% saline and imidazole buffer solution, and concluded that all crystalloid solutions appeared to exert a similar effect. We have recently completed a study in which a warmed (37 °C), buffered solution with a pH of 7.4 and electrolyte content similar to that of human plasma, except for calcium (Plasmalyte B), produced identical effects on coagulation to those seen with normal saline. Other workers in this field have shown that the calcium content does not appear to alter the observation of hypercoaguability produced by haemodilution.[2]

It would appear, therefore, that the answer to Williams' very pertinent question is that the nature of the crystalloid solution is unlikely to alter the observed effects of haemodilution, although we ourselves have not examined the effects of a non-electrolyte solution such as 5% dextrose.

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1. Tocantins LM, Carroll RT, Holburn RH. The clot accelerating effect of dilution on blood and plasma. Relation to the mechanism of coagulation of normal and hemophilic blood. *Blood* 1951; **6**: 720–739.
2. Egli GA, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DR. Effects of progressive haemodilution with hydroxyethyl starch, gelatin, and albumin on blood coagulation. *British Journal of Anaesthesia* 1997; **78**: 684–689.

Morbidity after day-case tonsillectomy in children

Editor,—Church, in his letter[1], comments on the high incidence of nausea and vomiting (40%) reported by Splinter and Rhine[2] and compares this with his own experience of a less than 5% incidence of this unpleasant complication. Splinter and Rhine in their response ponder on this difference when a very similar technique was used by both parties.

One explanation not mentioned in these letters is the duration of surgery. I believe that it is quite likely that a British tonsillectomy is of significantly shorter duration than a North American tonsillectomy. We even have some surgeons who can stretch a tonsillectomy and adenoidectomy to 1.5 h!

Years ago, I noted that postoperative nausea and vomiting (PONV) in paediatric surgical outpatients was less common after operations of short duration.[3] Decreased PONV associated with shorter anaesthesia has also been observed by Smith[4] and by Fahy and Marshall.[5] There are many factors which may influence the incidence of PONV, all of which must be considered when conducting studies, and especially when comparing the results from different centres. The influence of more prolonged anaesthesia on the incidence of PONV has not received the attention that it deserves.

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1. Church J. Morbidity after day-case tonsillectomy in children. *British Journal of Anaesthesia* 1998; **81**: 295.
2. Splinter WM, Rhine EJ. Prophylaxis for vomiting by children after tonsillectomy: ondansetron compared with perphenazine. *British Journal of Anaesthesia* 1998; **80**: 155–158.
3. Steward DJ. Experiences with an outpatient anesthesia service for children. *Anesthesia and Analgesia* 1973; **52**: 877–880.
4. Smith JM. Postoperative vomiting in relation to anaesthetic time. *British Medical Journal* 1945; **2**: 217.
5. Fahy A, Marshall M. Post anaesthetic morbidity in outpatients. *British Journal of Anaesthesia* 1969, **41**: 433–438.

Inhaled nitric oxide and the longitudinal distribution of PVR in ARDS

Editor,—I should like to comment on the article by Benzing and colleagues[1] who attempted to demonstrate the effects of inhaled nitric oxide on the longitudinal distribution of pulmonary vascular resistance (PVR) in ARDS. Their assertion is that nitric oxide affects pre- and post-capillary resistances with different dose responses, and their assumption is that both of these components of total PVR can be measured by analysis of the pressure–time curve after inflation of the balloon of a Swan–Ganz catheter. It is unfortunate, especially in view of their clear exposition of the argument as to the importance of the differential effects of pre- and post-capillary resistance in oedema formation in ARDS, that these assumptions cannot be supported because their measurement technique is flawed and their data are questionable.

Benzing and colleagues cite the work of Cope and colleagues[2] to support the technique. These investigators propose a model of the pulmonary vasculature based on an analogous electrical circuit (fig. 1A) comprising arterial and venous resistors in series (PVR_{art} and PVR_{ven}), a capacitor (pulmonary capillary capacitance, C_c) and a voltage source (pulmonary artery pressure, PAP). Disconnecting the voltage source (inflating the balloon) allows the capacitor to

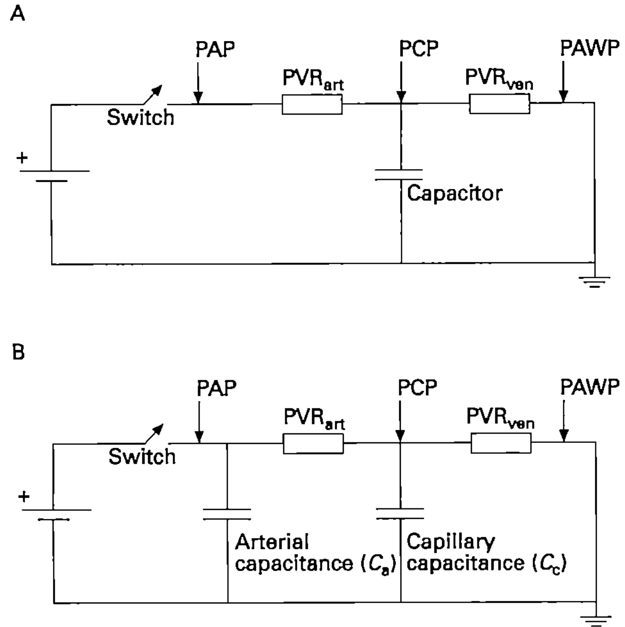

Figure 1 A· Cope and colleagues' equivalent circuit for current flow through the pre-(PVR_{art}) and post-(PVR_{ven}) capillary resistances. Note that in the circuit shown, when the switch is opened, current from the discharging capacitor flows only through PVR_{ven}, and the decaying voltage is described by a simple monoexponential function. B: Longitudinally separate compliances and resistances as the basis of a revised model are shown.

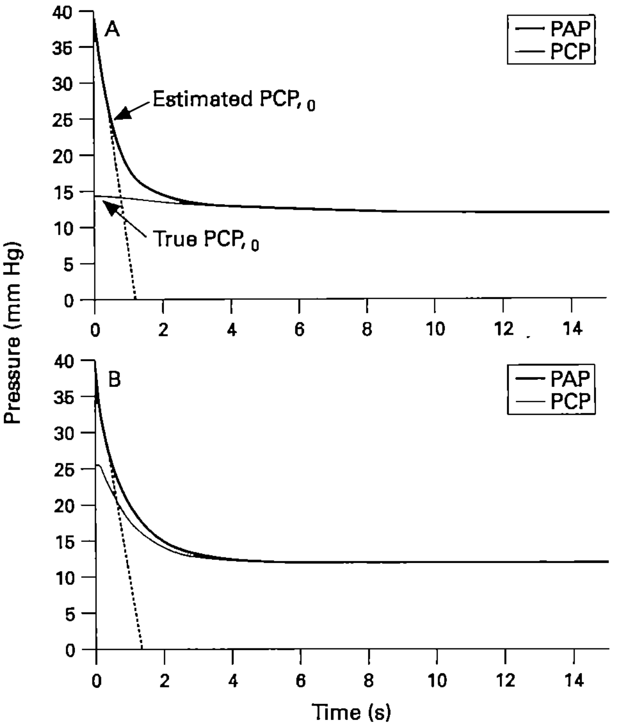

Figure 2 Plot of pulmonary artery occlusion pressure (PAP) and pulmonary capillary pressure (PCP) *vs* time after occlusion. In A, C_a=0.02, C_c=1, PVR_{art}=30 and PVR_{ven}=3. In B, C_a=0.1, C_c=0.2, PVR_{art}=3 and PVR_{ven}=3. All units are arbitrary and chosen to give a pressure decay time course similar to that observed.

discharge through the resistor, and allows the voltage to decay from the polarizing voltage to zero, just as pressure decays from PAF to pulmonary arterial wedge pressure (PAWP). For reasons for which there is no physical basis, the authors claim that the point at which the pressure changes from its rapid downstroke to its more gentle decay, represents pulmonary capillary pressure (PCP). They call this point the "point of inflection" and attempt to identify it by fitting a ruler through the curve by eye.

The mathematical definition of a "point of inflection" is the point on a function where the first-order derivative is maximum, that is the second order derivative equals zero. If Cope and colleagues' model is adopted, no such point exists since the discharge of a capacitor through a resistance (as in fig. 1A) is a simple exponential function, with a time constant equal to the product of capacitance and PVR_{ven}.

I have modified the model of Cope and colleagues in an attempt to produce a more complex exponential which might possibly underlie Benzing's attempt to dissect the function into component parts. I did this by adding another (pulmonary arterial) capacitor (C_a) to represent the elastance of the pulmonary arterial tree, as shown in figure 1B, since it is reasonable to assume that the pulmonary vasculature can be represented by an array of RC units. From this model, the total current flow through PVR_{ven} after opening the switch is given by the sum of the currents discharged from C_a and C_c.
Hence:

$$(\text{PCP}_{(t)}-\text{PAWP})/\text{PVR}_{\text{ven}}=C_c.\text{d}(\text{PCP})/\text{d}t+C_a.\text{d}(\text{PAP})\text{d}t$$

where $\text{d}(\text{PAP})/\text{d}t=(\text{PAP}_{(t)}-\text{PCP}_{(t)})/C_a.\ \text{PVR}_{\text{art}}$.

The symbolic solution to this is complex and so has been solved *gradatum* using a simple MS Excel spreadsheet, to plot PAP after balloon inflation for different values of PVR_{art}, PVR_{ven}, C_a and C_c for any given starting values of PAP and PAWP. The starting PCP is given by: $\text{PCP}_{(0)}=(\text{PAP}_{(0)}.\text{PVR}_{\text{ven}}+\text{PAWP}_{(0)}.\text{PVR}_{\text{art}})/\text{PVR}_{\text{art}}+\text{PVR}_{\text{ven}}$. The resultant time courses of $\text{PAP}_{(t)}$ and $\text{PCP}_{(t)}$ are shown in figure 2, where the starting pressures are set to values similar to those measured by Benzing and colleagues. In figure 2A, the values of C_a, C_c, PVR_{art} and PVR_{ven} are chosen to best resemble their published pressure–time curve and the ratio of C_c to C_a is 50:1. It can be seen that the true starting PCP differs considerably from the pressure at the "point of inflection". Note also that the actual ratio of PVR_{ven} to PVR has been set to approximately 0.1 in this example whereas Benzing and colleagues' estimation would be approximately 0.5. Only by making arterial and venous compliances and resistances similar, does the estimated PCP "appear" to approach the true value (fig. 2B) and even this is unsatisfactory because as both functions have similar time constants and boundary conditions, identification of a "point of inflection" is even more dubious.

Table 1 Estimated and actual PVR_{ven}/PVR values

PVR_{art} (all units arbitrary)	Estimated PVR_{ven}/PVR	True PVR_{ven}/PVR
30	0.519	0.09
15	0.371	0.166
Other input data		
PVR_{ven}	3	
C_a	0.02	
C_c	1	

It can also be shown from examination of series of these curves, that the estimated PVR_{ven}/PVR is *decreased* simply by reduction of PVR_{art}, which of course obligatorily *increases* the *actual* value of PVR_{ven}/PVR (table 1). Therefore, it is possible that in the subset of patients identified by Benzing and colleagues, the apparent effect of nitric oxide in reducing estimated PVR_{ven}/PVR was in fact artefactual, and mediated by a continued reduction in PVR_{art}.

In reality, the situation is probably much more complicated than either Cope's or my model can predict. Not only is the pulmonary circulation extremely heterogeneous (with an unknown distribution of parallel resistances), but compliance of the pulmonary capillaries no doubt changes in ARDS and may also be affected by nitric oxide. This affects the kinetics of PAP decay and alters the position of Benzing's "inflection point" independently of the longitudinal distribution of PVR. It is also probable that the kinetics of the measured PAP decay are influenced by the damping properties of the transducer system which were modified (possibly inconstantly) by addition of an air bubble.

In summary, while the possibility exists of a differential effect of nitric oxide on pre- and post-capillary resistances in ARDS which may be beneficial with regard to transcapillary fluid flux, the data of Benzing and colleagues are insufficient to support it.

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1. Benzing A, Mols G, Guttmann H, Kaltofen H, Geiger K. Effect of different doses of inhaled nitric oxide on longitudinal distribution of pulmonary vascular resistance in ARDS. *British Journal of Anaesthesia* 1998; **80**: 440–446.
2. Cope DK, Allison RC, Parmentier JL, Miller JN, Taylor AE. Measurement of effective pulmonary capillary pressure using the pressure profile after pulmonary artery occlusion. *Critical Care Medicine* 1986, 14: 16–22.

Editor,—We appreciate the interesting comments of Dr Farmery on our method used for estimation of pulmonary capillary pressure (PCP) in ARDS patients.[1] Determination of PCP in critically ill patients remains a subject of debate. However, most of the methods for PCP measurement which are used in experimental preparations, such as double occlusion pressure, micropuncture and the isogravimetric method, are not applicable in critically ill patients. To date, the only method for estimation of PCP in patients is analysis of the pulmonary artery pressure decay after balloon inflation.

Visual analysis of the pressure decay curve and determination of the "inflection point" have been used for PCP estimation in the past.[2-7] It is correct that in a mathematical sense, a point of inflection on a function is a point where the second derivative is zero. (The first derivative is not necessarily maximum, it also may be minimum.) That means a mathematical point of inflection is present in somewhat S-shaped curves or in trigonometric functions. On the contrary, the decay of pulmonary artery pressure after balloon inflation is not S-shaped but biexponential [8] A biexponential function does not have a point of inflection in the mathematical sense. Nevertheless, many of the authors using visual analysis of pulmonary artery pressure decay have named the point where the pulmonary artery pressure changes from a rapid to a more slow decay "inflection point". Therefore, we have adhered to this nomenclature.

Estimation of PCP by visual determination of the "inflection point" correlates well with other methods of PCP determination [9,10] Maarek, Hakim and Chang compared the double occlusion pressure technique (P_{do}) with PCP calculated by back extrapolation of the exponential pressure decay (*P*a0) and with visual determination of PCP from the pressure tracings (*P*a0+) in isolated canine lung lobes during pulsatile perfusion under various experimental conditions.[9] They found that both *P*a0 and *P*a0+ were good estimates of P_{do}, although *P*a0 values were slightly higher (mean 1.28 mm Hg) and visually determined *P*a0+ values were slightly lower (mean 0.67 mm Hg) than P_{do}. In quasi-intact dog left lower lobes, Hakim, Maarek and Chang compared P_{do} with extrapolated *P*a0 derived from an inflated pulmonary artery catheter and with visual *P*a0+ determination.[10] Double occlusion was performed manually. *P*a0+ was lower than P_{do}. Holloway and colleagues[2] compared visual analysis of pressure decay curves by determining the "inflection point" of the pressure decay with computer-reconstructed curves. They found an excellent correlation between both methods of analysis.

In our study, the "inflection point" was determined visually by placing a ruler on the rapid component of the pressure decline adjusted for the best fit and marking the point at which the slow component of the pressure profile deviated from the rapid component. Mathematically, a straight line was drawn through two points: (1) the point where pulmonary artery pressure starts to decrease after balloon inflation (*P*a(0) of equation (1), see below); and (2) one point of the fast component of pressure decay curve at time t_1. "Adjusting for the best fit" means that t_1 is varied in a manner that the slopes of the straight line and the rapid component of the pressure decay curves are quite similar. When t_1 reaches a point on the pressure decay curve where the difference between the slope of the pressure decay curve and the slope of the straight line becomes maximum, the deviation of the pressure decay from the straight line becomes visually most apparent. This point is marked as the "inflection point".

The time course of pulmonary artery pressure decay (*P*a(*t*)) and of pulmonary capillary pressure decay (*P*c(*t*)) are described by biexponential functions[8]·

$$Pa(t)=Ae^{\alpha t}+Be^{\beta t}+Pv \qquad (1)$$

$$Pc(t)=AK_{\alpha}e^{\alpha t}BK_{\beta}e^{\beta t}+Pv \qquad (2)$$

where *P*v=left atrial pressure and A, B, α, β, K_α and K_β=complex expressions which may be derived from pre-capillary (R_a) and post-capillary (R_v) vascular resistances, from pre-capillary (C_a), capillary (C_c) and post-capillary (C_v) vascular compliances, and from the transpulmonary pressure gradient at time 0 (*P*a(0)–*P*v).

A straight line which we have drawn for PCP estimation crosses the ordinate (*t*=0) at a *y*-value of:

$$Pa(0)=A+B+Pv \qquad (3)$$

The second point of the straight line at $t=t_1$ has a *y*-value of

$$Pa(t_1)=Ae^{\alpha t_1}+Be^{\beta t_1}+Pv \qquad (4)$$

The slope s_L of the straight line is a function of t_1:

$$s_L(t_1)=\frac{Pa(t_1)-Pa(0)}{t_1} \qquad (5)$$

Replacing *P*a(t_1) and *P*a(0) in equations (4) and (5) results in.

$$s_L(t_1)=\frac{Ae^{\alpha t_1}+Be^{\beta t_1}-A-B}{t_1} \qquad (6)$$

The slope $s_P(t_1)$ of the pulmonary artery pressure decay at time t_1 is the first derivative of equation (1) at t_1.

$$s_P(t_1)=A\alpha e^{\alpha t_1}+B\beta e^{\beta t_1} \qquad (7)$$

The difference D_S between the slope of the pressure decay $s_p(t_1)$ and the slope of the straight line $s_L(t_1)$ is a function of t_1 (for given R_a, R_v, C_a, C_c, C_v):

$$D_S(t_1)= A\alpha e^{\alpha t_1}+B\beta e^{\beta t_1}-\frac{Ae^{\alpha t_1}+Be^{\beta t_1}-A-B}{t_1} \qquad (8)$$

The difference between the slopes $D_S(t_1)$ is maximum when the first derivative of $D_S(t_1)$ (eqn (8)) is zero:

$$dDs(t_1)/dt_1=0 \qquad (9)$$

Differentiation of equation (8) and determination of t_1 from equation (9) is not trivial. Therefore, we have programmed equations (2), (6), (7) and (8) in a simple Excel 5 0 sheet according to the theoretical analysis of Bacconnier, Eberhard and Grimbert and have varied the values for R_a, R_v, C_a, C_v and C_c We then determined the time point t_1 where the difference of slopes was maximum. *P*a(t_1) as an estimate of P_c was then compared with the true *P*c(0) according to equation (2) (fig. 1).

In our patients, total pulmonary vascular resistance (PVR=R_{TOT}) varied from 90 to 350 dyn s cm^{-5} which is 0.068–0.263 mm Hg s ml^{-1} We have assumed that the balloon of the pulmonary artery catheter occludes a lobar artery. Thus the vascular resistance of the occluded vascular bed is approximately five times total pulmonary vascular resistance (i.e. 0.34–1.32 mm Hg s ml^{-1}). Human data for pulmonary vascular compliances, especially in ARDS, are not available. Vascular compliance measurements in dog lung lobes have yielded values of 1.35 ml mm Hg^{-1} [11] and ~0.065 ml mm Hg^{-1} kg body wt^{-1} with an arterial–capillary–venous

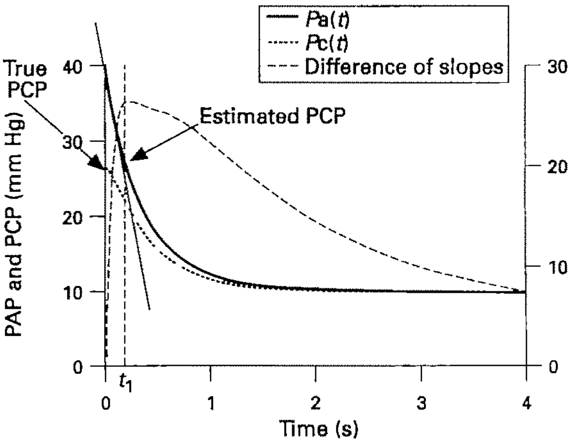

Figure 1 Visual analysis of pulmonary artery pressure (PAP) decay for determination of pulmonary capillary pressure (PCP). A straight line is drawn through two points of the pressure decay curve (*P*a(*t*)): (1) the point where PAP starts to decrease after balloon inflation (*P*a(0)); and (2) one point of the fast component of pressure decay curve at a time t_1. t_1 is varied in a manner that the slopes of the straight line and the rapid component of the pressure decay curves are quite similar. When t_1 reaches a point on the pressure decay curve *P*a(*t*) where the difference between the slope of the pressure decay curve and the slope of the straight line becomes maximum, the deviation of the pressure decay from the straight line becomes visually most apparent. This point is marked as the inflection point and is an estimate of PCP. Estimated PCP is comparable with true PCP (*P*c(*t*) at time 0) (see also text).

distribution of ~30:49:21.[12] If vascular compliance in humans is similar, lobar vascular compliance would be 4–4.5 ml mm Hg^{-1} for a 70-kg patient. In ARDS, vascular compliance must be lower as a result of vasoactive mediators,[11] pulmonary oedema and/or fibrosis.

We have performed a series of calculations: R_{TOT} was set at 0.4, 0.6, 0.8 and 1 mm Hg s ml^{-1}, C_{TOT} at 1, 2 and 3 ml mm Hg^{-1}, with a fixed arterial–capillary–venous distribution of 30:50:20, and Rv/R_{TOT} at 0.3, 0.4, 0.5, 0.6 and 0.7. $Pa(0)-Pv$ was fixed at 30 mm Hg, and Pv at 10 mm Hg.

The results of these calculations are shown in figure 2. The regression line between true and estimated PCP is $y=0.96x$ with a correlation coefficient of $r=0.95$. Thus estimated PCP underestimates true PCP but the error is relatively small. The observation that PCP estimation by visual analysis underestimates true PCP is in agreement with other studies.[9 10] The 95% confidence interval for the visual PCP determination is ~±1 mm Hg.[5] Therefore, we have classified patients as nitric oxide responders when PCP decreased by at least 2 mm Hg.[1]

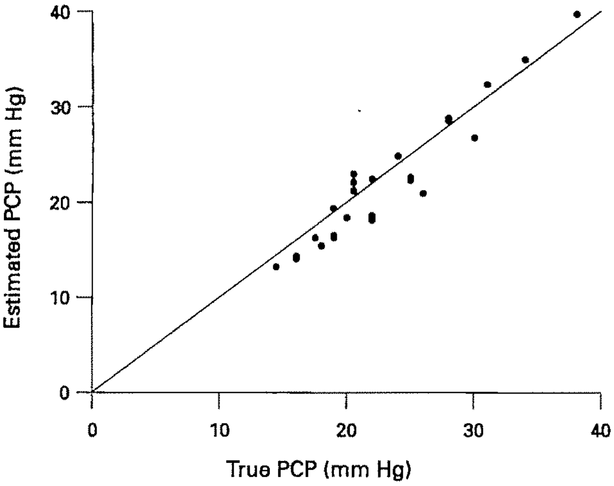

Figure 2 Comparison of estimated pulmonary capillary pressure (PCP) and true PCP for a variety of pulmonary vascular resistances, vascular compliances and different longitudinal distributions of pulmonary vascular resistance. The regression line is $y=0.96x$ with a correlation coefficient of 0.95. Thus estimated PCP slightly underestimated true PCP (mean 1.3 mm Hg).

Reducing pulse pressure by a small container with 0.4 ml of air increases compliance but does not change vascular resistance or longitudinal distribution of pulmonary vascular resistance. More importantly, pressure decay between diastolic pulmonary artery pressure and pulmonary artery wedge pressure (PAWP) should not be analysed but the decay between mean pulmonary artery pressure and PAWP should.[13] Therefore, we believe that visual analysis of pulmonary artery pressure decay, used in human studies, has some limitations, but is a good estimate of pulmonary capillary pressure. Our data[1] are also supported by our study demonstrating a decrease in transvascular albumin flux during nitric oxide inhalation.[14]

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1. Benzing A, Mols G, Guttmann J, Kaltofen H, Geiger K. Effect of different doses of inhaled nitric oxide on pulmonary capillary pressure and on longitudinal distribution of pulmonary vascular resistance in ARDS *British Journal of Anaesthesia* 1998; **80**: 440–446.
2. Holloway H, Perry M, Downey J, Parker J, Taylor AE. Estimation of effective capillary pressure in intact lungs. *Journal of Applied Physiology* 1983; **54**: 846–851.
3. Radermacher P, Santak B, Becker H, Falke KJ. Prostaglandin E_1 and nitroglycerin reduce pulmonary capillary pressure but worsen ventilation–perfusion distributions in patients with adult respiratory distress syndrome. *Anesthesiology* 1989; **70**: 601–606.
4. Cope DK, Parker JC, Taylor MD, Houston M, Taylor AE. Pulmonary capillary pressures during hypoxia and hypoxemia: Experimental and clinical studies. *Critical Care Medicine* 1989; **17**: 853–857.
5. Cope DK, Allison RC, Dumond ME, Taylor AE. Changes in pulmonary capillary pressure following cardiac surgery. *Journal of Cardiothoracic Anesthesia* 1988; **2**: 182–187.
6. Cope DK, Allison RC, Taylor AE. A simple method to determine pulmonary capillary pressure. *Anesthesiology* 1987; **67**: 866–868.
7. Isago T, Fujioka K, Traber LD, Herndon DN, Traber DL. Derived pulmonary capillary pressure changes after smoke inhalation in sheep. *Critical Care Medicine* 1991; **19**. 1407–1413.
8. Baconnier PF, Eberhard A, Grimbert FA. Theoretical analysis of occlusion techniques for measuring pulmonary capillary pressure. *Journal of Applied Physiology* 1992; **73**: 1351–1359.
9. Maarek JMI, Hakim TS, Chang HK. Analysis of pulmonary arterial pressure profile after occlusion of pulsatile blood flow. *Journal of Applied Physiology* 1990, **68**: 761–769.
10. Hakim TS, Maarek JMI, Chang HK. Estimation of pulmonary capillary pressure in intact dog lungs using the arterial occlusion technique. *American Review of Respiratory Diseases* 1989; **140**: 217–224.
11. Linehan JH, Dawson CA, Rickaby DA. Distribution of vascular resistance and compliance in a dog lung lobe. *Journal of Applied Physiology* 1982; **53**: 158–168.
12. Dawson CA, Rickaby DA, Linehan JH, Bronikowski TA. Distributions of vascular volume and compliance in the lung. *Journal of Applied Physiology* 1988; **64**: 266–273.
13. Cope DK, Allison RC, Miller JN, Parker JC. Estimation of pulmonary capillary pressure in intact dog lungs using the arterial occlusion technique. *American Review of Respiratory Diseases* 1990; **141**: 1602.
14. Benzing A, Bräutigam P, Geiger K, Loop T, Beyer U, Moser E. Inhaled nitric oxide reduces transvascular albumin flux in patients with acute lung injury. *Anesthesiology* 1995; **83**: 1153–1161.

Intrathecal diamorphine for postoperative analgesia after Caesarean section

Editor,—Husaini and Russell[1] found less postoperative itching and sedation in women who had intrathecal diamorphine 0.2 mg compared with morphine 0.2 mg mixed with bupivacaine for Caesarean section. They concluded that "there seems little reason to prefer morphine to diamorphine in the UK". I would like to take issue with this conclusion.

Diamorphine is presented only as a powder for reconstitution. The smallest mass of drug supplied is 5 mg, which must be appropriately diluted, and the correct volume of solution added to the bupivacaine. In contrast, preservative-free morphine is commercially available in the useful concentration of 2 mg in 10 ml. This may be conveniently offered to the anaesthetist to draw up 1 ml (for 0.2 mg) or 0.5 ml (for 0.1 mg), to which the desired volume of bupivacaine can be added. In the interests of minimizing the potential for drug error, particularly at emergency Caesarean section, the opioid which is ready to use seems vastly preferable.

Furthermore, morphine 0.1 mg compared with morphine 0.2 mg affords similar quality and duration of analgesia, with a reduced incidence of nausea and vomiting.[2] It would be interesting to establish whether diamorphine 0.1 mg has a better side effect profile than morphine 0.1 mg. However, even if diamorphine at this lower dose *were* shown to confer minor reductions in itching and sedation, I argue that this would not outweigh the risks inherent in the swift, accurate and aseptic preparation of the drug for intrathecal injection.

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1. Husaini SW, Russell IF. Intrathecal diamorphine compared with morphine for postoperative analgesia after Caesarean section under spinal anaesthesia. *British Journal of Anaesthesia* 1998; **81**: 135–139.
2. Milner AR, Bogod DG, Harwood RJ. Intrathecal administration of morphine for elective Caesarean section. A comparison between 0.1 and 0.2 mg. *Anaesthesia* 1996; **51**: 871–873.

Editor,—Dr Levy is correct when he suggests there is a small potential for a drug dose error because of the necessity to prepare the powdered diamorphine. But, in mitigation, this is a very straightforward dilution, even for a harassed anaesthetist. I am also grateful to him for drawing my attention to the availability of preservative-free morphine (2 mg in 10 ml); our pharmacy is unaware of its existence. Dr Levy has to consider the relative risk potential for an adverse outcome between diamorphine and morphine. Which has the greater risk to the patient—a drug dilution error with diamorphine while under the supervision of the anaesthetist or delayed respiratory depression in an unobserved patient?

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Editor,—We read with interest the study of Husaini and Russell[1] comparing intrathecal diamorphine and morphine for postoperative analgesia after Caesarean section under spinal anaesthesia. We recognize the value of this study in demonstrating the excellent postoperative analgesia that can be obtained using these drugs after such surgery and would encourage other obstetric anaesthetists to consider using the technique in their own practice.

Husaini and Russell suggest that intrathecal diamorphine may be superior to morphine for early postoperative analgesia after Caesarean section. Theoretically, this might be expected because of the higher lipid solubility of diamorphine providing a more rapid onset. However, their suggestions are based on the mean use of patient-controlled analgesia (PCA) morphine in the first 4 h after spinal anaesthetic; that is, an average morphine dose of 4.2 mg (median 2.5 mg) in those patients receiving intrathecal morphine compared with an average of 2.1 mg (median 1.5 mg) in those patients receiving intrathecal diamorphine. As stated by the authors, however, this result was not statistically significant. Furthermore, we do not believe these small amounts of morphine to be large enough to suggest a clinically important difference between the two groups. We would add our concerns that the initial set-up period of PCA use may involve administration of demonstration doses by carers and of "try it out" doses by the patient. Although these "inappropriate" doses are likely to be similar in the two groups we would recommend caution in interpretation of the amount of PCA opioid used in this initial period.

We would like to draw the authors' attention to our developing clinical experience of using intrathecal morphine and diamorphine for postoperative analgesia after Caesarean section. We have introduced this technique into our unit following recent personal experience (J.H.) at the Women's and Children's Hospital in Adelaide, South Australia, where intrathecal morphine has been used successfully for a number of years (diamorphine is not available for clinical use in Australia). We, like Husaini and Russell, are interested in the relative merits of morphine and diamorphine when used in this way. We now have an audited series of 24 patients who underwent Caesarean section under regional anaesthesia and received intrathecal morphine 150 μg (12 patients) or diamorphine 200 μg (12 patients). Half of the morphine group also received intrathecal fentanyl 10–15 μg. Additional postoperative analgesia was provided with diclofenac sodium 100 mg per rectum at the end of surgery and 50 mg orally three times daily thereafter. Oral paracetamol and codeine combinations were prescribed as required. All patients underwent uneventful surgery and none required intraoperative supplementation to their anaesthetic. As in the author's study, we found a higher incidence of pruritus in those given morphine compared with diamorphine although there was no difference in the incidence of nausea and sedation when assessed by nursing staff. Postoperative analgesia, however, appeared to be quite different between our two groups of patients. Our patients are regularly assessed by nursing staff in the first 24 h after operation using a verbal scale (none, mild, moderate or severe pain). In the morphine group, 11 of 12 patients had no pain or, at worst, mild pain. One patient developed moderate pain and no patient had severe pain. None of our patients who received intrathecal morphine required parenteral opioid after operation. In the diamorphine group, however, six of 12 patients had mild or no pain but six patients had moderate or severe pain. Two of these patients had severe pain, requiring rescue morphine i.v.

Why does our clinical experience of these techniques differ from the findings of Husaini and Russell? We suspect that the answer lies in the way postoperative analgesia is provided and the way patients are assessed. When using PCA morphine, patients tend to dose themselves until they find their own individual level of acceptable pain. There is no reason to expect that this acceptable level of pain differs between the two groups. Therefore, one would expect visual analogue scores (VAS) to be similar in each group irrespective of the intrathecal opioid used, although we accept that initially these scores may differ until PCA analgesia levels are established. Therefore, VAS levels are of limited value in comparing the two analgesic techniques in this situation but merely reflect similar access to analgesia in the two groups.

To compare the analgesic effects of the two techniques it is more pertinent, as in the study of Husaini and Russell, to examine the amount of postoperative opioid used. However, it is here where this study may be misleading. First is the provision of "as required" oral opioid. Although the number of patients using oral opioid was recorded in the study, the actual amount used was not documented. Thus there is uncertainty as to the total amounts of postoperative opioid received in several patients. Second, a large proportion of each group of patients failed to receive follow-up diclofenac on the prescribed regular basis, the reason often being that the patient felt comfortable. We feel that this influenced the amounts of PCA morphine administered in such a way as to mask any difference between the groups. Comfortable patients, declining diclofenac, may subsequently have become uncomfortable in the absence of the opioid sparing effects of non-steroidal analgesia resulting in increased PCA morphine use. The converse is that uncomfortable patients, accepting diclofenac, might then go on to use less morphine. Effectively, patients with good analgesia have been allowed to select themselves into becoming patients with poor analgesia and vice versa. This obviously has an unpredictable effect on PCA use and results in any differences between the two groups being more difficult to detect. We suggest future studies of this type should address these problems by limiting opioid availability to PCA with, if needed, titrated, documented i.v. rescue doses, and where not contraindicated, non-steroidal analgesia should be given to all patients irrespective of the level of pain at the time of dosing. This is more likely to be achieved by prescribing follow-up diclofenac by the oral route. We recognize the value of the study of Husaini and Russell in demonstrating the effectiveness of both intrathecal morphine and diamorphine for postoperative analgesia after Caesarean section. However, we remain sceptical that intrathecal diamorphine will prove as effective as morphine and believe further studies are required to clarify this issue.

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1. Husaini SW, Russell IF. Intrathecal diamorphine compared with morphine for postoperative analgesia after Caesarean section under spinal anaesthesia. *British Journal of Anaesthesia* 1998; 81: 135–139.

Editor,—I am very pleased that Drs Cutts and Hopkinson have shown so much interest in our article and in their encouragement of others to use intrathecal morphine or diamorphine for pain relief after Caesarean section.

They point out potential problems which may have influenced patient PCA use in the early postoperative period and suggest that these problems could account for the small difference and trend in PCA morphine use which we observed.[1] They go on to suggest that even if the trend towards more PCA use in the morphine group is true,[1] it is not clinically significant. To answer these points, demonstration PCA doses were not given by staff but the possibility of "try out" doses by patients cannot be ruled out. If such "inappropriate doses" were used, our data suggest no difference in behaviour between the groups: seven diamorphine and six morphine patients used no PCA morphine in the first 4 h and another three patients in each group used only one dose. I would not dispute the fact that the small difference between the group average doses of PCA morphine used in the first 4-h period is of little clinical significance but my anxiety is directed more towards those patients who make the larger PCA demands (e.g. 5 mg or more in the first 4 h): only two women in the diamorphine group but seven in the morphine group fell into this category. This difference between the groups in the numbers using larger amounts of PCA morphine just fails to achieve the usually accepted level of statistical significance (P=0.058) but nevertheless, I would suggest this is a clinically relevant difference in the early postoperative period.

Contrary to our findings, the audit being undertaken by Drs Cutts and Hopkinson suggests that morphine is superior to diamorphine and they wonder why their clinical experience is at odds with our study. I feel that the principal reason has been discussed already in our original article[1]: the use of a PCA is the only valid way of making a true comparison between different analgesia regimens. In their audit, pain is assessed on a verbal score by the midwives. Would different midwives at different times obtain similar pain assessments and, if they did, would they then set in motion the same response? How does the ward workload affect the response? It would also appear that parenteral opioids are not available routinely and rescue analgesia has to be provided by medical staff. Additionally, half of the morphine patients had intrathecal fentanyl and this is known to provide significant early postoperative analgesia but we are not told whether it was early or late when the difference between their morphine and diamorphine groups occurred. All of these individual points can introduce unknown confounding biases. In our study, although the doses of oral opioid used were not recorded it can be seen that compared with the diamorphine group, twice as many morphine patients used oral opioid but the VAS scores and PCA morphine demands were the same. In addition, almost identical numbers of patients in each group did not receive their full dose of diclofenac.

The importance of VAS scores is to ensure that patients in both groups attain a similar level of comfort because only then can a true comparison between the PCA requirements be made. If one group has higher VAS scores for pain and lower PCA demands than another group, then no reliable comparison of the PCA doses can be made. If one group has higher VAS scores and higher PCA demands, then again it is difficult to compare the groups but at least both differences are in the same direction and the real difference between the groups will be greater than a simple comparison of the PCA demands would suggest. The fact that, compared with the diamorphine group, the same, or more, morphine group patients used ancillary drugs does not support the suggestion that patients in our intrathecal diamorphine group are being "helped" so that their PCA demands are reduced to become equal to the demands in the morphine group. If anything, the contrary effect may be occurring.

The problem with administration of non-steroidal drugs is highlighted by Cutts and Hopkinson and I would agree that ideally these drugs should be given to all patients in the immediate postoperative period, irrespective of the presence or absence of pain. This was our intention but events conspired against us. We recognized the potential difficulties of ensuring regular administration of non-steroidal agents in the planning stage and diclofenac was not our first choice. Our first choice was to use oral piroxicam 40 mg at the end of surgery (given as Feldene melt). However, we were prevented from using piroxicam by the Ethics Committee on the basis of information present in the data sheets for the two drugs: the data sheet for piroxicam specifically stipulates "Feldene is not recommended for use in nursing mothers". The data sheet for diclofenac merely states that "traces of active substance have been detected in breast milk, but in quantities so small that no undesirable effects on the infant are to be expected". We chose the rectal route for diclofenac to circumvent potential problems with nausea and/or vomiting but the reluctance of British women for the rectal route was just as troublesome a problem.

We were most unhappy when we discovered that diclofenac had not been given as prescribed but the midwives countered by pointing out that the women who refused rectal diclofenac were comfortable. I can reassure Drs Cutts and Hopkinson that those women who did make the very high morphine demands all received prescribed diclofenac. Thus these women did not self-select and become uncomfortable because of the absence of an opioid sparing effect of diclofenac.

As pointed out in our article, the doses of PCA morphine used in both our study groups[1] were identical to the PCA morphine used in the diamorphine group in a previous study comparing intrathecal diamorphine with placebo after elective Caesarean section.[2] Apart from the slight doubts about the early postoperative period, I believe that our results, taken over these two studies,[1,2] indicate little difference in the analgesic properties between intrathecal morphine and diamorphine.

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1. Husaini SW, Russell IF. Intrathecal diamorphine compared with morphine for postoperative analgesia after Caesarean section under spinal anaesthesia. *British Journal of Anaesthesia* 1998; 81: 135–139.
2. Graham D, Russell IF. A double blind assessment of the analgesic sparing effect of intrathecal diamorphine (0.3 mg) with spinal anaesthesia for elective Caesarean section. *International Journal of Obstetric Anesthesia* 1997; 6: 224–230.

Flexible training and sex

Editor,—Patricia Scriven attempts to evaluate flexible (part-time) training in anaesthesia, and records a high degree of satisfaction.[1] She informs us that 96% of such trainees gave family commitments as the reason for wishing to train part-time; other reasons included "improved hours; disability and ill-health". The group characteristics of the study include no information on the sex of the trainees. As a former male part-time trainee, I submit that without this information the article cannot be regarded as an evaluation of flexible training, as all results presented are likely to be markedly influenced by sex.

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1. Scriven PM. Evaluation of flexible (part-time) training in anaesthesia. *British Journal of Anaesthesia* 1998; 81: 268–270.

Editor,—Thank you for allowing me to reply to Dr Dorrington's letter. The results reflected the flexible training scheme at the time of the survey The article recorded the evaluation of the scheme by all those in it, whether male or female. As far as I am aware, there are no published data detailing differences in satisfaction with anaesthesia training in the UK and gender.

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Induction of anaesthesia with sevoflurane and low-dose remifentanil: asystole following laryngoscopy

Editor,—We wish to describe the first reported case in an adult of asystole during intubation after inhalation induction with sevoflurane and remifentanil 0.5 μg kg^{-1}

A 65-yr-old man with stable angina pectoris was admitted to hospital for routine coronary artery bypass surgery. He had two vessel disease, with mildly impaired left ventricular function. His admission heart rate (HR) and mean arterial pressure (MAP) were 51 beat min^{-1} and 100 mm Hg, respectively. He gave no history of pre-syncope, syncope, vasovagal reactions or hypothyroidism. His angina symptoms were controlled medically with atenolol 50 mg daily, diltiazem 60 mg tid and isosorbide dinitrate 30 mg tid. These medications were continued up to and including the day of surgery. The patient was premedicated with lorazepam 3 mg. Anaesthesia was induced with vital capacity breaths of 5% inspired sevoflurane in oxygen. Loss of consciousness occurred uneventfully within 45 s, following which the inspired sevoflurane concentration was reduced to 3%. Heart rates before and after induction were 48 and 52 beat min^{-1}, respectively, and MAP values were 104 and 96 mm Hg, respectively. After loss of consciousness, rocuronium 0.6 mg kg^{-1} was given, and remifentanil 0.5 μg kg^{-1} was administered over 90 s, followed by infusion of 0.025 μg kg^{-1} min^{-1}. Over the next 2 min, HR and MAP decreased to 40 beat min^{-1} and 78 mm Hg. End-tidal sevoflurane concentration at this time was 2.2%. Immediately after laryngoscopy, the ECG changed abruptly from sinus rhythm to asystole. This was confirmed by the absence of a radial arterial pressure trace. One precordial thump was delivered, which resulted in a single ventricular complex. Atropine 0.6 mg was administered and followed by a second precordial thump, which successfully restored sinus rhythm, at a rate of 50 beat min^{-1}, with MAP 86 mm Hg. The total duration of asystole was 24 s. There were no acute ST-segment changes. The remainder of the anaesthetic was uneventful.

Vital capacity induction with sevoflurane in adults has been shown to be smooth and to maintain good cardiovascular stability with either no change, or an increase, in heart rate.[1,2] Bradycardia after gaseous induction in children with 8% sevoflurane has been reported, possibly reflecting relative over-dosage.[3] In our patient, HR increased from 48 beat min^{-1} before induction to 52 beat min^{-1} after induction. The end-tidal sevoflurane concentration before intubation was 2.2%. Sevoflurane is therefore unlikely to have contributed to the subsequent asystole.

Potent opioids are used frequently to reduce the pressor response to intubation, particularly in patients with ischaemic heart disease. However, potent mu agonists, fentanyl, alfentanil and sufentanil, can cause bradycardia and even asystole.[4–6] The mechanism is most likely a result of stimulation of the central vagal nucleus.[7] There is mounting evidence of the potential of remifentanil to cause severe bradycardia.[8,9] The timing of bradycardia and asystole in the case described coincided with the bolus dose of remifentanil, implicating this as the causative agent. A major predisposing factor in the patient was combined beta-adrenergic antagonist and calcium channel block therapy. Both classes of drugs have negative chronotropic effects which can be additive[10] Asystole occurred after potentiation of the vagotonic effects of laryngoscopy by remifentanil, in a patient whose sinoatrial activity was already severely depressed and who was unable to mount a balanced sympathetic response.

This case is reported to highlight the potential of remifentanil to cause severe bradycardia. When given in combination with beta-adrenergic and calcium channel block, even a relatively low dose of remifentanil, as used in this case, can result in asystole.

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1 Yurino M, Kimura H. Vital capacity rapid inhalation induction technique: comparison of sevoflurane and halothane. *Canadian Journal of Anaesthesia* 1993; 40: 440–443.
2. Muzi M, Robinson BJ, Ebert TJ, O'Brien TJ. Induction of anesthesia and tracheal intubation with sevoflurane in adults. *Anesthesiology* 1996; 85· 536–543.
3. Townsend P, Stokes MA. Bradycardia during rapid inhalation induction with sevoflurane in children. *British Journal of Anaesthesia* 1998; 80: 410.
4. Egan TD, Brock-Utne JG. Asystole after anaesthesia induction with a fentanyl, propofol, and succinylcholine sequence. *Anesthesia and Analgesia* 1991; 73: 818–820
5. Maryniak JK, Bishop VA. Sinus arrest after alfentanil. *British Journal of Anaesthesia* 1987; 59: 390–391.
6. Starr NJ, Sethna DH, Estafanous FG. Bradycardia and asystole following the rapid administration of sufentanil with vecuronium *Anesthesiology* 1986; 64: 521–523.
7. Reitan JA, Stengert KB, Wymore ML, Martucci RW. Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. *Anesthesia and Analgesia* 1978; 57: 31–36.
8. Schuttler J, Albrecht S, Breivik S, Osnes S, Prys-Roberts C, Holder K, Chauvin M, Viby-Mogensen J, Mogensen T, Gustafson I, Lof L, Noronha D, Kirkham AJT. A comparison of remifentanil and alfentanil in patients undergoing major abdominal surgery. *Anaesthesia* 1997; 52: 307–317.
9. Hogue CW, Bowdle TA, O'Leary C, Duncalf D, Miguel F, Pitts M, Streisand J, Kirvassilis G, Jamerson B, McNeal S, Batenhorst R. A multicentre evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery *Anesthesia and Analgesia* 1996; 83: 279–285.
10. Packer M, Meller J, Medina N, Yushak M, Smith H, Holt J, Guererro J, Todd GD, McAllister RG, Gorlin R. Haemodynamic consequences of combined beta-adrenergic and slow calcium channel blockade in man. *Circulation* 1982; 65: 660–667.

Aprotinin therapy and disseminated intravascular coagulation after hip replacement

Editor,—We read the case report by Logan regarding a patient who developed disseminated intravascular coagulation after the use of polymethacrylate bone cement during a revision hip replacement and died shortly after.[1] We wish to report an almost identical case in which the use of aprotinin resulted in correction of haemostatic failure.

A 90-yr-old female known to have aortic stenosis (gradient 50 mm Hg) and left ventricular hypertrophy underwent a left revision hip replacement under general anaesthesia with continuous central venous pressure and arterial pressure measurement. The intraoperative course was unremarkable apart from episodes of hypotension after induction and after cement insertion which required treatment with metaraminol. Approximately 90 min after cement insertion and while the patient was in the postoperative recovery area, another episode of hypotension occurred (68/43 mm Hg) and this was associated with a decrease in central venous pressure from 8 to 1 mm Hg. Inspection of the wound revealed blood seeping through the dressing; the wound drain had rapidly filled with another 450 ml of blood. A clotting screen at that time revealed a prothrombin time four times normal, activated partial thromboplastin time 98 s, platelet count 56×10^9 litre^{-1} and haemoglobin concentration 8 g dl^{-1}. Over the next 45 min, despite 4 units of FFP, 2 units of platelets and 6 units of blood, the bleeding continued and repeat studies confirmed ongoing consumption coagulopathy. A test dose of aprotinin 50 ml was administered and this was followed by continuous infusion at 50 ml h^{-1} for the next 11 h Within 40 min of commencing this therapy, clot formation was noted for the first time and the requirement for blood/colloid replacement was reduced. In total, 17 units of blood were transfused. The rest of the recovery period was uneventful and further FFP and platelets were not required.

Aprotinin is an inhibitor of proteolytic enzymes, including plasmin. Clinical studies have demonstrated or suggested a protective effect against haemorrhage in surgical situations which have included liver transplantation and vascular surgery.[2] In this case, where a severe coagulopathy was associated with polymethacrylate bone cement and hip surgery, we observed rapid reversal of haemostatic failure and would advocate its use in similar circumstances.

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1. Logan SW. Death associated with disseminated intravascular coagulation after hip replacement. *British Journal of Anaesthesia* 1998; 80: 853–855.
2. Murphy WG, Davies MJ, Eduardo A The haemostatic response to surgery and trauma. *British Journal of Anaesthesia* 1993; 70: 205–213.

Editor,—Drs Higgins and Brayshaw were presented with a similar clinical scenario to the one I outlined, except that there were no features of myocardial ischaemia. In the case I described, death could probably have been avoided had it not been for the pre-existing myocardial ischaemia, as it was this, rather than the coagulopathy, which was directly responsible for her death. They managed to control the haemorrhage by adding aprotinin after initial administration of clotting factors. Seventeen units of blood were administered so the improvement did not appear to be immediate, although they did not state if further coagulation tests were performed.

The use of aprotinin in this situation has not been described; all previous studies regarding its use in orthopaedic surgery[1–5] have started the infusion before the onset of bleeding and of these, two did not show a statistically significant reduction in blood loss.[4,5] Kallis and colleagues[6] suggested there was a benefit if aprotinin was given after commencement of bleeding when fibrinolysis and platelet membrane glycoprotein 1b activation have occurred. The cause of the bleeding after orthopaedic joint surgery has not been as fully studied as in cardiopulmonary bypass,[7] although hyperfibrinolysis is known to occur and therefore aprotinin may be efficacious if given in this situation. Aprotinin is relatively free of adverse effects but is known to cause anaphylaxis,[7,8] and in orthopaedic patients has caused deep vein thrombosis after operation.[4] Therefore, I feel the use of aprotinin should be reserved as a last resort when administration of clotting factors have not stabilized the situation, as in this case.

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1. Capdevila X, Calvet Y, Biboulet P, Biron C, Rubenovitch J, d'Athis F. Aprotinin decreases blood loss and homologous transfusions in patients undergoing major orthopedic surgery. *Anesthesiology* 1998: 88: 50–57.
2. Murkin JM, Shannon NA, Bourne RB, Rorabeck CH, Cruikshank M, Wyle G. Aprotinin decreases blood loss in patients undergoing revision or bilateral total hip arthroplasty. *Anesthesia and Analgesia* 1995; 80: 343–348.

3. Janssens M, Joris J, David JL, Lemaire R, Lamy M. High dose aprotinin reduces blood loss in patients undergoing total hip replacement surgery. *Anesthesiology* 1994; 80: 23–29.
4. Thorpe CM, Murphy WG, Logan M Use of aprotinin in knee replacement surgery. *British Journal of Anaesthesia* 1994; 73: 408–410.
5. Hayes A, Murphy DB, McCarroll M. The efficacy of single dose aprotinin 2 million KIU in reducing blood loss and its impact on the incidence of deep venous thrombosis in patients undergoing total hip replacement surgery. *Journal of Clinical Anaesthesia* 1996; 8: 357–360.
6. Kallis P, Tooze JA, Talbot S, Cowans D, Bevan DH, Treasure T. Aprotinin inhibits fibrinolysis, improves platelet adhesion and reduces blood loss. Results of a double blind randomised clinical trial. *European Journal of Cardio-Thoracic Surgery* 1994; 8: 315–322.
7. Royston D Preventing the inflammatory response to open-heart surgery: the role of aprotinin and other protease inhibitors *International Journal of Cardiology* 1996; 53 (Suppl.): S11–37.
8. Schulze K, Graeter T, Schaps D, Hausen B. Severe anaphylactic shock due to repeated application of aprotinin in patients following intrathoracic aorta replacement. *European Journal of Cardio-Thoracic Surgery* 1993; 7: 495–496.

Laryngeal mask and tonsillectomy

Editor,—We read with interest the letter from Dr Venn[1] which highlighted a complication of the use of the laryngeal mask airway (LMA) during tonsillectomy in an adult male. He described snaring of the pilot balloon tubing by the surgeon which caused it to be severed and the LMA cuff to deflate during the surgical procedure. The consequences of such an event in the presence of intra-operative tonsillar haemorrhage, we agree, can be serious.

It is essential, therefore, that the anaesthetist is fastidious when inserting the LMA after induction, ensuring that it is the correct size for the patient, does not rotate on insertion, remains seated in the midline and is adequately secured. Once inserted, it is then our practice to align the flexible LMA tubing together with the pilot tubing in the midline over the lower incisors and lip, and secure them firmly, taking care to avoid any slack which would allow either of the tubes to drift and potentially become trapped by the Boyle–Davis gag or, in this case, the snare. If this technique is adhered to, we see no reason to resort to taping the pilot tubing to the main tubing of the mask.

Indeed, this method of taping may alter the unique characteristics of the reinforced LMA that make it so adaptable in its use. During the manufacture of the LMA, the main tubing, which is composed of silicone, is formed separately from the pilot tubing and unlike a tracheal tube, the pilot tubing is not incorporated into the main construction, as this would lead to a reduction in the flexibility of the LMA, the very nature of which makes it ideal for intra-oral surgery. It has also been reported that the mask may become obstructed by the Boyle–Davis gag; this is usually a result of the LMA being too large or too large a blade on the gag being selected.[2]

We cannot stress enough, therefore, that when the airway is shared between anaesthetist and surgeon, both need to be extra vigilant to ensure airway patency.

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1. Venn PJH. Use of the laryngeal mask during tonsillectomy. *British Journal of Anaesthesia* 1998; 81: 298–299.
2. Nair I, Bailey PM. Review of the uses of the laryngeal mask in ENT anaesthesia. *Anaesthesia* 1995; 50: 898–900.

Editor,—I was interested to read the report of surgical damage to the pilot tube while using a laryngeal mask for airway maintenance during tonsillectomy.[1] Dr Venn is incorrect in asserting that this complication has not been reported previously, however.

My colleague and I encountered an almost identical situation during tonsillectomy on a 15-yr-old girl. In our case, the problem came to light when the surgeon handed the severed end of the pilot tube to the scrub nurse along with the first tonsil. Fortunately, the laryngeal mask continued to perform its function with atmospheric pressure only in the cuff, the larynx was not soiled and there was no evidence of airway obstruction. Therefore, we were able to complete the case without replacement of the laryngeal mask.

An awareness of the recommendation to secure the pilot tube alongside the stem of the laryngeal mask, made in our report,[2] may have prevented the further incidence of this unfortunate complication.

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1. Venn PJH. Use of the laryngeal mask during tonsillectomy. *British Journal of Anaesthesia* 1998; 81: 298–299.
2. Short JA, Melillo EP. Damage to a laryngeal mask during tonsillectomy. *Anaesthesia* 1997; 52: 507.

Editor,—Thank you for the opportunity to reply to Drs Porter and Bailey and Dr Short on my correspondence about a complication while using a flexible laryngeal mask airway for tonsillectomy.

I note that a similar complication was reported by Short and Melillo in 1997. I presume that in their case the pilot tube had sealed while being transected, thus maintaining pressure in the cuff with no change in the patency of the airway. This does sometimes occur and is a good reason to use a syringe to deflate the cuffs of tracheal tubes rather than cutting the pilot tube before extubation. The case I reported demonstrates that this will not always happen.

While I welcome the comment made by Porter and Bailey regarding vigilence when inserting the laryngeal mask for shared airway cases, I do not fully understand their reservations about taping the pilot tube to the main tube. I presume the altered characteristics to which they refer relate to possible tension on the pilot tube which might displace the mask during movement of the head and neck. While I accept that this is possible, if the pilot tube is taped without tension, and assuming the same arc exists as immediately before insertion of the Boyle–Davis gag for tonsillectomy, I think this is unlikely to happen. However, I entirely agree that avoiding any slack in the pilot tube is the key to avoiding complications when sharing the airway.

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British Journal of Anaesthesia 1998; **81**: 997–1000

BOOK REVIEWS

Problems in Anesthesia. Management of Acute Pain, Vol. 10, No. 1. J. A. GRASS (editor). Published by Lippincott-Raven, Philadelphia. Pp. 135; indexed; illustrated.

The title of this volume is perhaps not entirely accurate, for while many anaesthetists are associated with the provision of acute pain management, it is really a problem for everyone involved with patient care and not just a problem in anaesthesia! However, by the development of anaesthesia-based acute pain services, it is often assumed that we have taken the problem under our umbrella. As such, one supposes that we can consider it as a problem in anaesthesia.

There are an ever increasing number of books available on acute pain management and so it was with interest that I opened the cover to see what particular slant was to be taken in this small volume which is published as part of a quarterly series. Would this book concentrate on a better holistic care for the patient with concomitant benefits with regard to acute pain, or would it concentrate on the technical aspects of care? The answer soon becomes apparent; a significant part of the book (more than 10%) deals with the economics of acute pain management in the USA, or to be more precise, the income that acute pain services can generate. The first and last chapters paint a rather depressing picture (at least to me) of the development of acute pain services over the years that have generated income, followed more recently by a decline in funding and a struggle for survival. The changes in reimbursement by insurers in the USA has lead to a real threat to the goose that so far has laid the golden eggs. The days when acute pain services were a useful form of income generation seem to be on the wane and physicians are clearly concerned regarding the impact both on the institution and on their own well-being. However, the conclusion is that even if acute pain services are unable to generate income for a hospital or individual physicians, there is still a good argument for having them on humanitarian grounds. As such, therefore, many of our colleagues in the USA are now having to use the same arguments as we have for years to justify investment in acute pain management.

Financial considerations aside, the remainder of the volume contains chapters on most aspects relating to acute pain management. The contents are fairly predictable as all groups of drugs and different techniques are covered. In general, the quality of the chapters is very good and up-to-date, although there is great variability. While there are some excellent chapters, including those on pathophysiology and novel neuraxial analgesics, other chapters have little new to enlighten the reader. However, is it really fair to blame the chapter authors as, while there have been fascinating developments in the pathophysiology of pain and in the development of new novel analgesics, there is precious new to report with regard to patient-controlled analgesia?

Overall, if one ignores the economics aspect which may not be of great interest to the non-US anaesthetist, this small volume contains a generally good series of review articles on important aspects of acute pain management. It ranges from simple information to complex considerations, and overall it is pitched at about the right level. While it may not satisfy the acute pain connoisseur, it will certainly be of value to the novice, particularly if they like "analgesic recipes" which are provided in abundance.

M. Harmer

Respiratory Measurement. G. HEDENSTIERNA. Published by BMJ Publishing Group, London. Pp. 172; indexed, illustrated.

This book is not just about measurement; in fact, it makes a fairly good textbook of respiratory physiology. There are three major headings: (i) physiological principles in health and chronic disease, (ii) anaesthesia and acute respiratory failure and (iii) the practice of respiratory measurement. Thus, strictly speaking, only the third section, approximately half of the book, is about how to measure gas volumes, gas exchange and mechanics

Certainly, a great deal of the basic physiology and measurement required for trainee anaesthetists is covered. The sections on acute respiratory distress syndrome (ARDS) are, as one would expect, particularly good. I enjoyed being put right on one of my old favourites, "pursed lip" breathing in the emphysematous patient. Hedenstierna points out that the familiar explanation, that PEEP applied in this way "stabilises" the airway, cannot be true as it implies an increased pleural pressure and therefore, in itself, no change in airway dynamics. The real explanation is that pursing the lips increases lung volume and airway calibre, slowing the flow rate and lessening the decrease in pressure that causes airway collapse.

The illustrations are mostly adequate but there is a very poor representation of a nitrogen single breath test, which contains a deal of illustrator's licence. On the same section, it seems an omission not to point out that the reason why the nitrogen test can be used to measure anatomical deadspace but not physiological deadspace is that nitrogen does not take part in gas exchange. And a few lines further on, it is a pity that more space is not dedicated to a more thorough explanation of that perennially misunderstood artefact, the arterial-end-tidal $P\text{co}_2$ difference.

Surprisingly, it is not always obvious where to look in the index; compliance, for instance, is listed under ventilation mechanics rather under the C's.

My major niggle is with the English in the text In common with all educated Swedes, Dr Hedenstierna's spoken English is excellent. But that is no guarantee of excellently written scientific English. I just wish that the series editors (C. E. W. Hahn and A. P Adams) had spotted some of the many examples of poor, or at best, spoken English, that adorn the text. Some readers may find themselves, as I was, being diverted in their reading in order to search for more acceptable expressions. Editorial revision would have improved clarity, and probably saved a few words too.

R. Fletcher

Anaesthesia. Essays on its History. J. RUPREHT, M. J. VAN LIEBIG, J. A. LEE AND W. ERDMANN (editors). Published by Springer-Verlag, Berlin. Pp. 424; indexed; illustrated. Price US$55. Dutch Gld. 110.

This book is a reprint of the proceedings, first published in 1985, of the 1st International Symposium on the History of Modern Anaesthesia held in Rotterdam in 1982. The word "modern" is significant, for few go back earlier than the 1920s. In their preface the editors state that the "nestors of anaesthesia" gave them support and encouragement in their task. This unusual expression is found only in the 20-volume *Oxford English Dictionary* and this claims that it originates from the Homeric hero famous not only for his age but also for his wisdom.

The editors have not attempted to impose uniformity of style but have allowed each speaker a free rein, a luxury that can rarely be afforded. The resulting variety of styles, coupled with the different ways in which the speakers have interpreted their briefs, makes absorbing reading. The essays are short, each only 2–4 pages in length. Some are personal reminiscences and such "witness accounts" often have great advantages over a historian's analysis written at a later date. They tell an inside story that may not be recorded in formal publications, if at all. They have an immediacy, a sense of time and place and tell of how ideas progressed among those who participated. But they too have disadvantages They presuppose that the writers are good communicators who can indeed transmit a flavour of the time. More importantly, memories are fickle and highly selective, some more so than others. There may be a temptation to edit recollections in the light of subsequent events. Happily, the organizers of this symposium were wise in their selection of contributors and few of these disadvantages are seen.

Outstanding are Morris' account of the worldwide influence of Ralph Waters, perhaps not always appreciated this side of the Atlantic, Gray's insight into how he came to realize the potential of neuromuscular block and Hunter's personal story of the evolution of neuroanaesthesia. All tell marvellous inside stories, as does Macintosh's account of how the Nuffield chair in Oxford was achieved in spite of, rather than because of, the academics, and almost entirely because of the vision of Nuffield himself. Mansfield's "Reminiscences of anaesthesia during the Blitz and 10 happy years in India" is just as exciting and graphic as its title suggests. Several papers, including that of Vermeulen-Cranch, the first professor of anaesthesia in continental Europe, give insight into why anaesthesia in Europe lagged for so long behind that in Britain and America, while Killian points out that the 1st German

Anaesthesia Congress in 1927 was attended almost entirely by surgeons and pharmacists. Lee philosophizes on the advances of his time, while Hopkin uses hindsight to puzzle out why the "lytic cocktail" did not quite catch on.

Other contributors have chosen to give a history of their topic rather than a personal account, and for the most part these are well done and adequately referenced from primary sources. Only one writer is a pure historian and surprisingly, his own essay eschews reference to original sources and quotes only from his own publications. The breadth of historical knowledge shown by many of the anaesthetist–historians is impressive. Wilson shows how anaesthesia spread throughout Australasia exactly in the wake of increasing opportunities for travel to, from and within that vast continent Inamoto describes Hanaoka's first general anaesthetic in Japan in 1805 and the impacts between western and oriental medicine following the Meiji revolution in 1868. Haddad shows the influence of French medicine in the Middle East brought about by the Napoleonic wars. Nearer home, the start of a regional society might not seem promising material, but Smith encapsulates the whole post-war scene in anaesthesia in telling it. Astrup's scholarly account of the development of blood-gas and acid-base measurements is purely historical and makes no mention of the part he himself played.

This is not a definitive history of anaesthesia nor is it written by or for historians, although the latter will find it a valuable source book. Rather it is by those with a keen historical sense writing for today's anaesthetists, for we can only understand the present against the background of the past. Minor criticisms are that I should have liked more biographical data about the authors themselves and that the index is unreliable

The Rotterdam symposium was described as "the happiest meeting ever". It has been followed by three more and by the founding, in USA and Britain respectively, of the Anaesthesia History Association and the History of Anaesthesia Society. A parallel development is that many professional historians are now specializing in the history of medicine and making important contributions. The rigours of historical research are no less than those of science, though they are rather different. This collection of essays shows not only the value of the personal story told by one who was there, but also the special insight into past events that can be given by the amateur clinician–historian who accepts the discipline of historical research. There is a place for all. Today's anaesthetists will find much in this volume that is enlightening, thought-provoking and enjoyable.

A. K. Adams

Handbook of Drug Interactions. L. Karalliedde and J A. Henry (editors). Published by Arnold, London. Pp. 935; indexed. Price £55 00.

This handbook is a detailed guide to the interactions that can occur between different drugs used in medical and psychiatric practice; a considerable proportion of the text (approximately one-seventh) is devoted to interactions between anaesthetic agents and other drugs. Although the book contains contributions from 30 different authors (including 19 anaesthetists), the editors have succeeded in integrating the text in a relatively consistent and seamless manner, so that differences in style are not readily apparent.

The handbook essentially consists of 37 sections; each has a common format and is devoted to interactions involving a single drug or group of drugs. Most sections begin with a short summary of the pharmacology and interactions of a group of drugs, this is succeeded by a series of individually referenced monographs describing specific drug–drug interactions. Each monograph describes the effects of the interaction, discusses the pharmacological mechanisms involved, and comments on its implications and clinical significance. The book has an extensive bibliography, and more than 2500 references are cited in the text.

In common with most handbooks, this volume appears to be primarily designed for reference purposes, rather than reading from cover to cover. Nevertheless, a reviewer has his duty to do, and in my opinion the book as a whole is well-presented and contains a great deal of extremely useful information. I was particularly impressed by the sections on antibiotics, antiviral drugs and anticoagulants. Although many of the individual monographs ambitiously attempt to explain drug–drug interactions in terms of the biochemical or pharmacological mechanisms involved, these are often unknown or obscure The publishers suggest that a key feature of the book is the minimal use of complex pharmacological terminology. In my view, this is not entirely true. For instance, many interactions involving drug metabolism are explained in terms of effects on the isoforms of hepatic cytochrome P_{450}; not all may be entirely conversant with this complex multi-enzyme system.

The handbook includes the generic names of many drugs, and I was interested in the editors' approach to their nomenclature For some time, prescribers of drugs (including contributors to the *British Journal of Anaesthesia*) have been encouraged to use their recommended international non-proprietary names. In contrast, this book generally uses British approved names, with the United States approved names in parentheses. Unfortunately, this approach, as in other textbooks, is the source of some confusion. Thus the section on local anaesthetics contains separate monographs for amethocaine and tetracaine, one is the British approved name and the other the international non-proprietary name for the same drug.

The text contains several small errors At one point, gamma amino benzoic acid is abbreviated to GABA; there is also some confusion between acetylcholinesterase, anticholinesterases and anticholinergic drugs. In addition, there are a relatively large number of typographical errors. Nevertheless, this book contains a lot of reliable information and deserves a place among the established reference texts on drug interactions.

T. N. Calvey

FRCA Survival Guide. S. M. Yentis. Published by Butterworth-Heinemann, Oxford. Pp. 109; indexed; illustrated. Price £12.99

I really enjoyed reading Dr Yentis's book. It is easy to read, short and has a very chatty style. It also has occasional illustrations/cartoons that are a little variable and that are certainly not as good as the text.

The book is divided into nine chapters and deals with all aspects of the FRCA: a good "introduction", "how to plan revision", "the MCQs", "the essays" (only half a page as they no longer feature in the examination!), "SAQs" (sorry, short answer questions), "vivas", "OSCEs", "sitting the exam" and "after it's all over" are the chapter headings. There is an appendix that lists some topics for a comprehensive revision plan and there is also a useful index.

The book is full of sensible and helpful advice to the examination candidate and gives excellent ideas on improving skills in all parts of the tests. Although there is little that is new in the text, it is the collation of so much advice into one small book that makes it so attractive

Having read a book of this type, there is a need for the candidate to ensure that they have the latest rubric from the Examinations Department at the Royal College of Anaesthetists, as the FRCA is constantly changing the goalposts. There are already some changes to the MCQs and OSCE for the primary examination for example, so it is crucial for the candidate to keep up to date and Dr Yentis stresses this himself in the introduction.

No matter which part of the examination one is sitting, this book is worth reading. I expect many examiners will buy it too It is a pleasant read which should become mandatory for all examinees. Perhaps if I had been able to buy such a book, years ago, I would not have taken so many attempts at the Primary myself!

D. J. Wilkinson

Anesthesia Equipment Manual. M. B. Sosis (editor). Published by Lippincott-Raven, New York. Pp. 354; indexed; illustrated. Price £65.00.

This book is a compilation of 25 chapters, written by a group of 22 contributing authors, the vast majority being clinical anaesthetists. All are American, and so this manual is aimed unashamedly at the American anaesthetist.

The editor, Mitchel Sosis, includes in his preface the statements "Anesthetists use what may appear to be a bewildering array of equipment in their daily course of providing anesthesia to their patients"; "The safety of an anesthetised patient may depend just as strongly on the anesthetist's ability to maintain proper operation of the equipment that is being used, as it does on his or her knowledge of pharmacology or physiology"; and "This handbook has been prepared with these points in mind to clearly explain and illustrate the entire spectrum of anesthesia equipment". The British reader may readily agree with the first two statements, but the main question when reading this book is to decide whether or not this handbook meets the editor's aim "to clearly explain and illustrate the entire spectrum of anesthesia equipment".

Maybe it was unwise for the editor to put such a bold aim in print in the opening page of the book, since it encourages the reader to find out just what is missing from the text. Broadly speaking, the book covers the anaesthetic machine itself (nine chapters); anaesthesia ventilators (one chapter); clinical monitoring equipment (four chapters) and then a pot-pourri of chapters covering equipment for the practice of clinical anaesthesia (for example airway management, paediatric anaesthesia, maintenance of normothermia, etc) (11 chapters).

Another "off the cuff" remark in the preface states that "Up to now even the works that have attempted to deal with this subject (anaesthesia equipment) in a comprehensive fashion were not user friendly". This prompts the reviewer to compare Mitchel Sosis' book with those which are already freely available, such as Dorsch and Dorsch's *Understanding Anesthesia Equipment*; Clayton Petty's *The Anesthesia Machine*; Ward's *Anaesthetic Equipment*; and even Hutton and Prys-Roberts' *Monitoring in Anaesthesia and Intensive Care*, since the book under review devotes several chapters to monitoring equipment. In fact, I was in two minds here, since I found the above mentioned comparator books user-friendly, even if it is impossible for any book to achieve the status of being "comprehensive".

Without being pedantic, some specific points can be made. The first nine chapters of Sosis's book are written in conjunction with Clayton Petty, and they cover the same subject matter (including inevitably many of the diagrams) as the book, *The Anesthesia Machine*, written by Clayton Petty Similarly, the chapters on clinical monitoring cannot hope to compare with the Hutton and Prys-Roberts' book, which devotes 440 pages to this important topic. The remaining chapters, although adequate and generally well-written, do not illustrate the *entire spectrum of anesthesia equipment*. This is not the fault of the individual authors, who were only fulfilling their contractual obligation. But the editor has made some surprising omissions considering that the book was published in 1997 and we are living in a modern electronic and computer age.

Some examples are as follows: the first chapter on "flow meters" should really be headed "rotameters"; there is no mention of modern mass-flow control systems, as used in modern anaesthetic machines, for example the Engstrom ELSA, the PhysioFlex or the Datex Engstrom AS/3; nor are modern electronically controlled vaporizers adequately described. The whole description of the anaesthetic machine, in this book, is a parochial description of current American machines and past technology. Even the chapter describing conventional vaporizers makes no mention of the dangers of over-filling these devices. One could go on relentlessly. There is little or no mention of humidifiers, sterilization, oxygen concentrators, depth of anaesthesia assessment, etc. All of these topics should surely be present in an up-to-date textbook which claims to be "comprehensive". These topics are certainly referred to in the older, competing, textbooks referred to above. Even the chapter on electrical hazards, surely a well-worn subject, contains only two paragraphs on microshock and very little on diathermy current burns.

Perhaps this reviewer has concentrated too much on the claims and statements made in the preface, but that is what the book is going to be judged by. All in all, I do not believe that this book adds a great deal to what has already been written in the other standard textbooks, some of which are much more up-to-date (for example, Ward's *Anaesthetic Equipment*) and far more relevant to the British anaesthetist.

One final point concerns the title of this book and, to a lesser extent, the titles of other similar anaesthetic equipment books. Although the title of Sosis's book is *Anesthesia Equipment Manual*, the book is concerned entirely with the conventional inhalation anaesthesia machine and its associated equipment. There is no mention of total i.v. anaesthesia, the concept of target-controlled infusion or patient-controlled analgesia. Only a few lines are devoted to the infusion of fluids throughout the entire book and there is no description of drop counters, infusion pumps or syringe drivers. Since we are rapidly approaching the new millennium, surely it is time for authors either to title their books appropriately or else include a substantial section on total i.v. anaesthesia and patient-controlled analgesia if they are going to use generic titles such as *Anesthesia Equipment* when publicising and describing their books?

C. E.W. Hahn

Clinical and Resuscitative Data, A Compendium of Acute Medical Data, 5th Edn. R. Dunnill and P. Colvin. Published by Blackwell Science, Oxford. Pp. 204; indexed; illustrated. Price £19.95. ISBN 0-86542-788-7.

At the beginning of their career, the anaesthetic trainee is presented with what at first might appear to be an insurmountable task. They must master new technical skills, operate increasingly complex equipment and absorb and retain many facts, figures, protocols and algorithms. The nature of the specialty often requires prompt, if not immediate, action making reference to library or reading room impractical. To assist the trainee, many anaesthetic "pocket books" and *aide-mémoires* have been published. This is such a book.

The title of this text may suggest it to be a reference book that will contain multiple tables and innumerable lists of various anaesthetics, pharmacological, physiological and physiochemical values ranging from the mundane to the esoteric. However, as stated in the preface, this is a clinical text and not a comprehensive and exhaustive collection of data. It covers a diverse range of topics: anaesthesia, critical care and pharmacology, to name but a few The common medical emergencies are covered with treatment algorithms that, where comparable, are in accord with those offered by such bodies as the European Resuscitation Council or the Association of Anaesthetists of Great Britain and Ireland. The reference tables for physiological variables are more than adequate. Resuscitation algorithms are included, as indeed they should be. This will inevitably present problems, resuscitation guidelines are revised more frequently than books, so rendering it impossible for textbooks to remain up to date. I was pleased by the section on local anaesthesia which, together with dermatomes and urotomes, gives details of appropriate agents and doses of local anaesthetics for particular types of block.

The facts are accurate and the information is clearly presented. The cost of this clarity is brevity, the depth is shallow. Brevity cannot be accounted for solely by a need to remain "pocket sized". This book is significantly slimmer than many other similar texts and has too many blank pages. A text of this type should be topical and up to date. References to drugs which are of historical interest only, such as curare, cyclopropane and phenformin, are out of place.

That this book is in its fifth edition is a testament to its previous success. This edition is 40 pages shorter than the previous one and has lost little as a result of this trimming. Most of my criticisms are minor; any book that attempts to condense such a diverse range of topics into 204 pages will never do it to everyone's satisfaction The authors have not tried to reproduce a larger text in diminutive guise. It fills its niche well but it is not a replacement for the larger standard texts. It will appeal to the anaesthetic novice and other theatre personnel. It will be of most use as a readily available reference source in the back pocket, briefcase or handbag, and not perched on a book shelf. Its value will be determined as much by what the owner does with it as what it contains. This is of course true of any textbook.

D. P. L. Atherton

Injury in the Young. M. P. Ward Platt and R. A. Little (editors) Published by Cambridge University Press, Cambridge. Pp. 317, indexed; illustrated. Price £55.00.

The editors state in the preface that the purpose of the book is to bring together current knowledge about injury in childhood. The contributors were asked to review experimental and empirical data which influence the rational management of such injuries. It is aimed at clinicians and researchers who work with injured children. It is not intended as a text of paediatric trauma or as a clinical handbook. The term "injury" is used in a broad sense, including elective surgery, lung injury associated with ARDS, and neonatal chronic lung disease All but two contributions are from the UK, with one each from Canada and the USA.

The 15 chapters vary in length, style and emphasis. Most can be read as self-contained review articles. There are short chapters on "Epidemiology of trauma involving children", "Emergency room requirements", "Child deaths in the A&E department" and "Children's rights and child protection". There are longer chapters on "Immediate life support", "Evaluation of injury", "Wound healing", "The lung after injury" and "Metabolic and endocrine stress responses to surgery". Three chapters discuss various aspects of head injury and two chapters are devoted to burns. There is a comprehensive chapter on near drowning by D. Bohn from Toronto.

There is much valuable information in this volume. It is well produced, with clear illustrations, extensive references and a good index However, taken as a whole, the content is somewhat disjointed. Some chapters are chiefly concerned with pathophysiology ("Injuries of the developing brain", "The lung after injury").

Others place more emphasis on clinical management. Some aspects of injury are covered in depth (for example, the two chapters on burns are excellent reviews on the acute response to thermal injury and nutritional support). Other aspects receive scant attention (for example, fluid resuscitation regimens, timing of surgery, infection control and pain management in burns). Skeletal, spinal and visceral injuries are covered briefly in the resuscitation and evaluation chapters but are not discussed in detail. There is no chapter on transport of injured children, either within the hospital or between hospitals. Paediatric anaesthetists will be frustrated that the improvements in paediatric pain management of the past decade do not receive more discussion in a book of this nature. However, the sections of the book which focus on pathophysiology are a welcome stimulus to research minded clinicians.

Severe paediatric trauma cases are not common, even in a regional paediatric centre. Furthermore, many patients present initially to district hospitals. Few individual clinicians acquire substantial experience of all categories of paediatric trauma. This book will be a valuable addition to institutional and departmental libraries in hospitals faced with childhood injuries. Most chapters can be recommended to PICU consultants and trainees. Anaesthetists will find some sections of the book interesting and useful, but there are better sources for the anaesthetic management of paediatric trauma. In future editions, the appeal of the book would probably be increased by commissioning some additional chapters. For example, fluid resuscitation regimens have become a hot topic and deserve more scrutiny! It would also be helpful to consider the problem of running multicentre therapeutic studies, given the relatively low frequency of specific injuries in children.

R. E. Sarginson

British Journal of Anaesthesia 1998; **81**: 1001

ERRATA

Does speed of intrathecal injection affect the distribution of 0.5% hyperbaric bupivacaine? (BJA 1998; 81: 355–357). p357, Reference No. 9: The title of the reference was incorrect. It should read:

9. Greene NM. Update and elimination of local anesthetics during spinal anesthesia. *Anesthesia and Analgesia* 1983; **62**: 1013–1024.

EDITORIAL III. Mathematical coupling in medical research: lessons from studies of oxygen kinetics (BJA 1998; 81: 118–120).

The y-axis of figure 1A was incorrect. The correct version of figure 1 is given below.

We apologize to the authors for these errors, which arose during the editorial process.

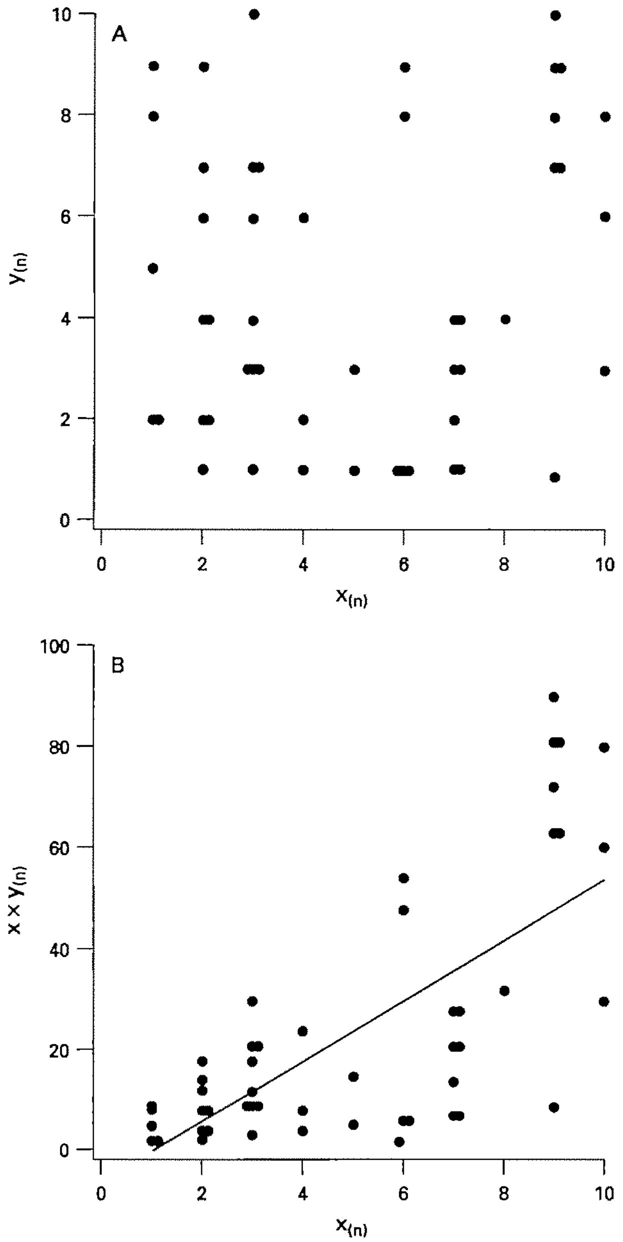

Figure 1 (A) Plot of 50 pairs of random numbers, $x_{(n)}$ and $y_{(n)}$, between 1 and 10. (B) Using the same random number data pairs, a third variable $x.y_{(n)}$, the product of $x_{(n)}$ and $y_{(n)}$, is positively correlated with $x_{(n)}$ when re-plotted. This occurs because of mathematical coupling.

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